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Syntheses and Applications of Trifluoromethyl- and Pentafluorosulfanyl-Containing Organic Molecules

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SYNTHESES AND APPLICATIONS OF TRIFLUOROMETHYL- AND PENTAFLUOROSULFANYL-CONTAINING ORGANIC MOLECULES

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ABSTRACT

Fluorinated organic compounds have received great attention and even play a key role in human daily life. Now up to 30% of agrochemicals and 20% of all pharmaceuticals contain one or more fluorine atoms. The development of more atom-economic efficiency and green procedures for the introduction of fluorine atoms and fluorine-containing groups into organic molecules has gained increasing interest lately. The focus of this work is to introduce the highly electronegative and lipophilic trifluoromethyl (CF_3-) and pentafluorosulfanyl groups (SF_5-) into organic substrates.

New and convenient routes for the preparation of the widely used trifluoromethylation reagents trifluoromethyltrimethylsilane ($TMSCF_3$) and potassium (trifluoromethyl)trimethoxyborate [$CF_3B(OMe)_3^-K^+$] using fluoroform (CF_3H) as the trifluoromethyl source were successfully developed. Dimsyl-K, freshly prepared from potassium hydride (KH) and dimethyl sulfoxide (DMSO), was applied to activate the "chemically inert," but low-cost and abundant CF_3-group source, fluoroform (CF_3H). Direct trifluoromethylation with CF_3H avoided the use of an ozone-depleting reagent, such as bromotrifluoromethane (CF_3Br) or iodotrifluoromethane (CF_3I). Furthermore, the transformation of a chemical waste like CF_3H into valuable fluorochemicals is highly desirable.

In addition, a synthetic route to the "super-trifluoromethyl group"-containing building block pentafluorosulfanyl difluoroacetic acid [$SF_5CF_2C(O)OH$] was developed. The addition of SF_5Br to chlorotrifluoroethylene in the presence of a radical initiator gave

1-pentafluorosulfanyl-1,1-difluoro-2,2,2-fluorochlorobromoethane. Then oxidation of this adduct, followed by hydrolysis gave the desired pentafluorosulfanyldifluoroacetic acid in 82% yield. The pentafluorosulfanylperfluoroalkyl halides SF_5CF_2I, $SF_5CF_2CF_2Br$, and $SF_5CF_2CF_2I$ were also prepared for use in the syntheses of other SF_5-containing compounds. For example, convenient syntheses were developed for the hydro compound $SF_5CF_2CF_2H$ from either of the latter two reagents. Furthermore, the synthesis of fullerene (C_{60}) derivatives bearing a pentafluorosulfanyl group was investigated by using both of the aforementioned SF_5-containing perfluoroalkyl iodides. *Bis*-1,7-$(SF_5CF_2CF_2)_2$-C_{60} was selectively synthesized and isolated via collaborative work with the research group of Drs. Strauss and Boltalina at Colorado State University. In addition, the halogen bonding effect was demonstrated from mixtures of pentafluorosulfanylperfluoroalkyl halides and Lewis bases in pentane solution.

DEDICATION

I dedicate my dissertation to my supporting and ever faithful family. A special feeling of gratitude to my loving mother Xiaobo Zou whose words of encouragement and push for tenacity ring in my ears to move forward. My father Dr. Feng-Ling Qing, you always provide me the freedom and advice to pursue my dream. My adored paternal and maternal grandfathers Jian-Gong Qing and Ruo-Song Zou left me a remarkable and memorable childhood at the beautiful hometown, XinTianPu.

I also dedicate this dissertation to my friends and appreciate the help from Minghu Wang, Yang Yang and Ye Yang to overcome the difficulties for adapting to the study and life in the United States. All my friends in Clemson, Qingzhao An, Yifei Jiang, Junyan Ma, Yu Shen and Bohua Wu, you always share your happiness and support me throughout the process. I must give special thanks to Sheng Peng for sharing experience and attention.

Lastly, I dedicate this dissertation to my beloved girlfriend Yutung Chen, your company is my sources of inspiration and motivation to complete this journey.

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CHAPTER ONE

DIRECT TRIFLUOROMETHYLATION

1.1 Introduction

1.1.1 Properties of Trifluoromethylated Compounds

Fluorine, the chemical element with the highest electronegativity, naturally exists in the form of cryolite (Na_3AlF_6), fluorite (CaF_2), and fluorapatite [$Ca_{10}(PO_4)_6F_2$]. These rich and common minerals in the planet's crust led fluorine to being ranked as 24th in universal abundance and 13th in terrestrial abundance.[1] Despite the natural abundance of fluorine, few organic molecules exist containing such strong C-F bond (**Table 1-1**)[1] in nature.[2-8] The fact can be explained by both the low solubility of the nature sources of fluorine (cryolite, fluorite, and fluorapatite) and the limited nucleophilicity of inorganic fluoride under a mild environment, which further blocks the possibility to deliver a fluorine atom to an aqueous biological system.[8]

Table 1-1. *Properties of fluorine, trifluoromethyl group, and others*[1,15]

X	H	O	Cl	Br	I	N	F	CH_3	CF_3
Electronegative (Pauling Scale)	2.1	3.5	3.2	2.8	2.5	2.5	4	2.3	3.2
Van der Waals Radius (Å)	1.2	1.52	1.75	1.85	1.98	1.98	1.47	2.23	2.74
C-X bond Length (Å)	1.09	1.43	1.77	1.9	2.1	2.1	1.35	1.51	1.49
C-X bond Dissociation Energy (KJ/mol)	420	351	328	301	218	356	490	377	431

In 1810, Ampère first suggested fluorine as an element, which was found to be difficult and dangerous to isolate and separate from its minerals. In fact, several early experimenters were reported to have either been severely injured or died during their attempts. Until 1886, Moissan finally isolated elemental fluorine via the low-temperature electrolysis of a 1 to 12 mixture of potassium fluoride (KF) and hydrogen fluoride (HF) in a U-shaped Pt tube.[9-10] From then on, fluorine was found to be the lightest halogen, and it exists as a pale yellow, highly toxic, diatomic gas at standard conditions. Meanwhile, it is the most electronegative and extremely reactive element, even noble gases can form fluoride compounds. As fluorine gas was used to enrich uranium, the Manhattan Project in World War II brought the rapid development of fluorine chemistry. Fried's first successful synthesis of an organic fluorine-containing compound, 9-fluoro-hydrocortisone acetate, indicated a new era of fluorine in biological chemistry in 1954 (**Figure 1-1**).[11] The activity of this fluorine-containing acetate is 11 times greater than that of the corresponding non-fluorinated parent compound because of the lower pK_a of the 11β-OH group and thus the increased ability of this group to donate a hydrogen bond, i.e., increased oxidative resistance to metabolic inactivation. Now, approximately 20-30% of modern pharmaceuticals, such as Lipitor, Odanacatib, and Prozac (**Figure 1-2**), [3-4,6,8] and

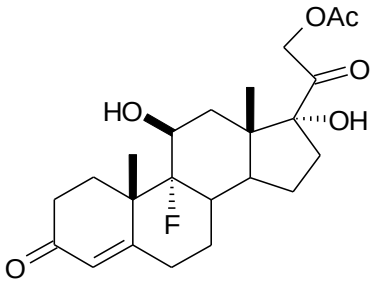
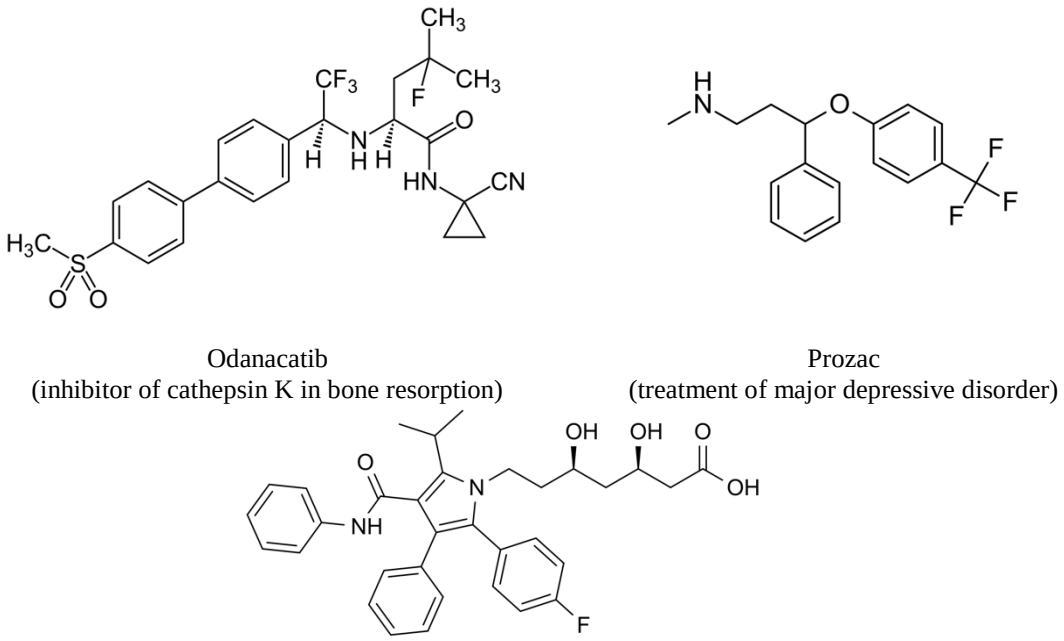


Figure 1-1. *9-Fluoro-hydrocortisone acetate.*[11]

agrochemicals contain fluorine atoms because of the enhanced lipophilicity, membrane permeability, receptor-binding selectively, and oxidative resistance. It is therefore not surprising to witness the highly increasing demand to introduce one or more fluorine atoms into drug candidates. Rapidly increasing efforts have been undertaken to discover more efficient methods, reagents, and catalysts for the transfer of a fluorine atom or fluorine-containing functional group, such as the trifluoromethyl (CF_3) group, through nucleophilic, electrophilic, and radical methods to desired organic substrates with various structures in the past decades.[12-14]



Odanacatib
(inhibitor of cathepsin K in bone resorption)

Prozac
(treatment of major depressive disorder)

Lipitor
(lipid-lowering agent)

Figure 1-2. *Examples of fluorine-containing drugs.*[3-4]

The trifluoromethyl group is unique to other alkyl groups in that it has a much larger electronegativity (at 3.2, equal to that of chlorine, **Table 1-1**);[12,15] it has a strong electron-

withdrawing nature, a large hydrophobic domain, low polarizability, and highly inert carbon-fluorine bonds [E(C-F) = 116 kcal/mol].[15] The CF_3 group is also a strong σ- ($-I_\sigma$) and π-acceptor ($-I_\pi$) in *α,β*-unsaturated systems. The negative hyperconjugation of the CF_3 group causes the electron density at the *β*-carbon atom to be decreased. A rapidly increasing demand exists to adjust the properties (acidity, dipole moment, polarity, lipophilicity, and chemical/metabolic stability) of pharmaceuticals and agrochemicals via introduction of this special group. Such as Prozac (shown in **Figure 1-2**), an antidepressant drug that has a six-fold increase in activity over its non-fluorinated analogue in selective inhibition of the uptake of serotonin.[3-4] Trifluoromethylated compounds are also widely used in agrochemical and materials science.[16] Moreover, the trifluoromethyl group is used to mimic the carbonyl group, and the generated CF_3-containing molecule is often more stable.[3]

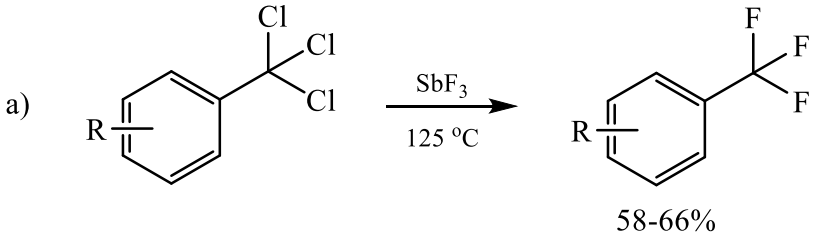
1.1.2 Synthesis of CF_3-containing Molecules

Trifluoromethyl-containing molecules are not found in the natural world, and thus these compounds are only available by organic synthesis. The traditional strategies for the preparation of CF_3-containing molecules have two approaches: (1) either the formation of a C-F bond through the direct fluorination of a functional group, such as in the Swarts reaction,[17] or (2) the intense development of trifluoromethylation methodologies wherein a new C-C bond is formed using commercially available CF_3-containing building blocks.[18]

This latter category includes three different mechanisms: electrophilic, radical, and nucleophilic trifluoromethylations.[19-21]

1.1.2.1 Halogen Exchange Chemistry

The replacement of chlorine (or heavier halogens) in target organo-halogen molecules by fluorine through the use of antimony trifluoride (SbF_3) was discovered and refined by Swarts in 1892, and thereafter such a reaction was named as the Swarts reaction. Antimony trifluoride can be used for the exchange of sufficiently reactive halogen atoms such as benzylic halogens (**Scheme 1-1**, Path a).[17] For example, the benzotrichlorides applied as starting material shown in Path a can be easily prepared via Friedel-Crafts alkylation or free-radical chlorination.[22] Trichloro-aliphatics are much less reactive in the original Swarts reaction with SbF_3. The conversion of the trivalent antimony partly or totally into the pentavalent state by the addition of chlorine, bromine, or $SbCl_5$ can increase the reactivity of SbF_3.[23] As shown in Path b in **Scheme 1-1**, 1,1,1-trifluoroethane is synthesized from 1,1,1-trichloroethane with a mixture of SbF_3 and $SbCl_5$ at a relative low temperature. The Swarts reaction is still applied in industry to produce chlorofluorocarbons



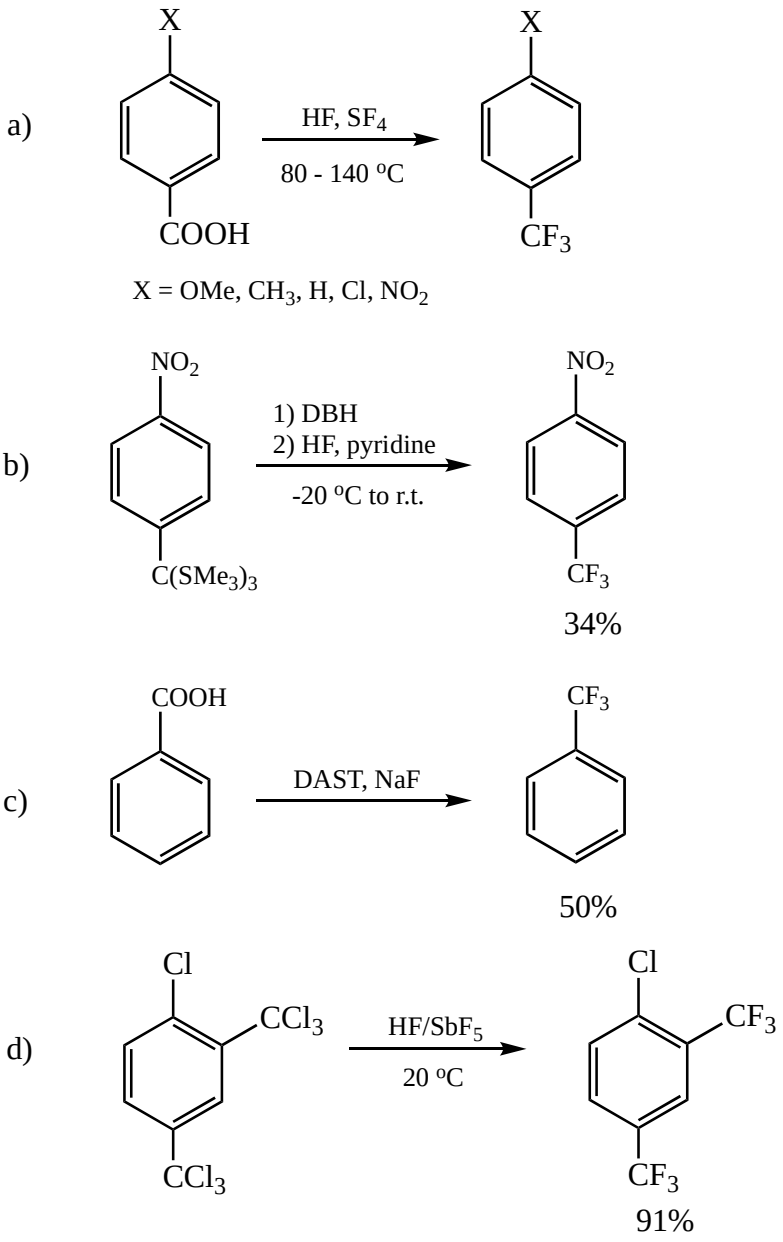
Scheme 1-1. *Swarts reaction.*[22-23]

(e.g., dichlorodifluoromethane), which now must be totally consumed as intermediates due to the Montreal Protocol from 1987. Due to the increasing health concerns on the usage of toxic antimony trifluoride, a mixture of $AlCl_3/FCCl_3$ or hydrogen fluoride is more often used now as the substituting fluoride source.[24]

Carboxylic acid derivatives can also be applied as starting materials to react with SF_4 and XeF_2 to produce trifluoromethylated compounds. For example, *para*-substituted benzotrifluorides can be synthesized from the reaction of sulfur tetrafluoride with *para*-substituted benzoic acids (**Scheme 1-2**, Path a).[25] The stronger electron-withdrawing ability of a substituent on the ring can increase the yields of the respective benzotrifluoride derivative. Meanwhile, the yield can also be increased by using of an excess amount of hydrogen fluoride (HF) under mild reaction conditions. Trifluoromethyl-containing aromatic compounds can also be obtained by the treatment of aromatic orthothio esters with either *N*-bromosuccinimide (NBS) or 1,3-dibromo-5,5-dimethylhydantoin (DBH) followed by the HF/pyridine complex (**Scheme 1-2,** Path b).[26] Benzotrifluoride can also be prepared by heating benzoic acid with diethylaminosulfur trifluoride (DAST) in the presence of sodium fluoride (NaF) (**Scheme 1-2**, Path c).[27] Anhydrous HF can also fluorinate benzotrichloride to benzotrifluoride as shown in Path d of **Scheme 1-2**, with antimony pentafluoride (SbF_5) being used as a catalyst in order for the reaction to proceed under milder conditions than with HF alone.

However, all of the reactions mentioned above are environmentally unfriendly and suffer from poor atom-efficiency. For example, six equivalents of hydrogen fluoride (HF) are often consumed to generate one equivalent of the trifluoromethyl group. Moreover, the

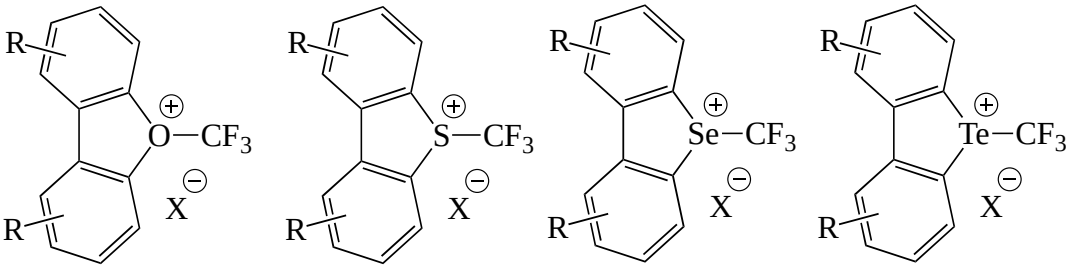
harsh reaction conditions further limit the application of these halogen exchange reactions on functional groups.



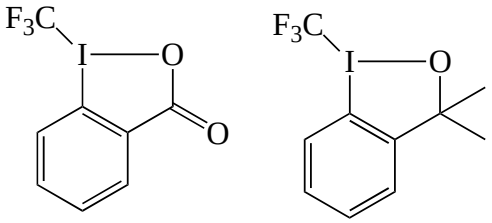
Scheme 1-2. *Synthesis of benzotrifluoride from functional group fluorination.*[25-27]

1.1.2.2 Electrophilic Trifluoromethylation[28,29]

A method to generate the highly energetic trifluoromethyl cation (CF_3^+) has been a challenge in the history of organofluorine chemistry.[30] Yagupolskii first discovered an electrophilic perfluoroalkylation reagent in 1984.[31] This was demonstrated by the effective trifluoromethylation of sodium 4-nitrobenzenethiolate by a *S*-trifluoromethyl diaryl-sulfonium salt. From then on, two types of electrophilic trifluoromethylation reagents have been developed. Umemoto *et al*. first introduced the trifluoromethyl chalcogenium salts,[32] while later, Togni *et al*. developed a class of neutral hypervalent iodine reagents. (**Figure 1-3**).[33]



Dibenzochalcogenium salts



Togni's trifluoromethylation reagents

X = TfO^-, BF_4^-, SbF_6^- R = H, NO_2, *t*-Bu

Figure 1-3. *Electrophilic trifluoromethylation reagents.*[30-33]

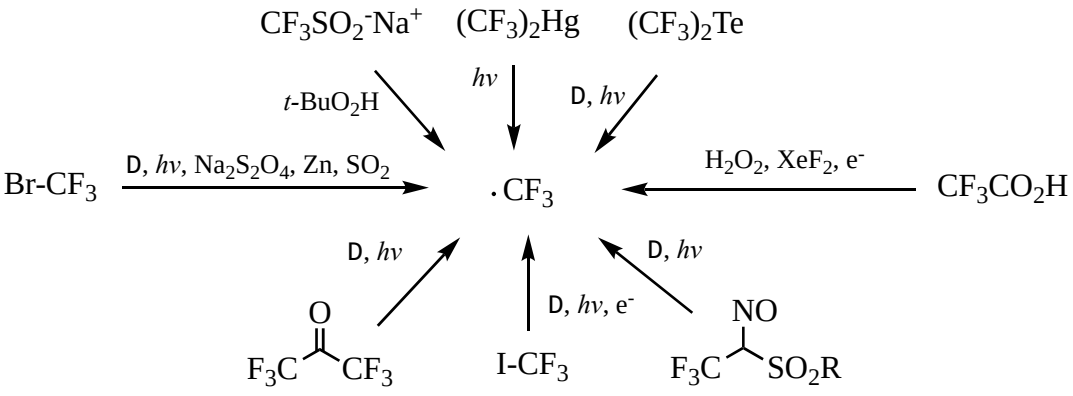
The trifluoromethyl chalcogeniums opened a new era to trifluoromethylation chemistry. In the early 1990s, Umemoto and coworkers achieved a breakthrough in the preparation of heterocyclic analogues of diarylsulfides, dibenzochalcogenium salts. The importance of these reagents is that the reactivity can be selectively modified by adjusting the electron-withdrawing and electron-donating substituents on the benzene rings. For example, the reactivity of these reagents increases when electron-withdrawing groups are applied, such as with nitro (NO_2) and sulfonate (SO_3^-) groups.[34] In addition, the trifluoromethylating ability enhances from tellurium to selenium to sulfur. However, this kind of reagent can only be used on the trifluoromethylation of *C*- and *S*-centered nucleophiles.[35] Only *O*-(trifluoromethyl)dibenzofuranium salts generated *in situ* can transfer a CF_3-group to nucleophiles with *N*- and *O*-centers.[36] During the past two decades, both the synthesis of (trifluoromethyl)dibenzochalconium salts and the reaction conditions for electrophilic trifluoromethylation have been developed and optimized, but the synthesis of these salts remains complex and requires highly expensive and reactive regents, such as trifluoromethanesulfonic anhydride, $(CF_3SO_2)_2O$.

Meanwhile, Togni's reagents, reported in 2006, have been proven to be the most useful reagents for the electrophilic trifluoromethylation onto *C*-, *S*-, *P*-, and *O*-centered nucleophilic substrates.[37] Furthermore, Togni's reagents have been utilized by an increasing number of research groups in the rapidly growing field of transition-metal-catalyzed electrophilic trifluoromethylation. Recent results include the copper-catalyzed trifluoromethylation of inactivated terminal olefins, alkynes, (hetero)aryl- and alkenyl-boronic acids, and indoles.[38-40] But the preparation of Togni's reagents require highly

expensive iodide precursors. The direct electrophilic trifluoromethylation on hard nucleophiles, such as amines, phenols, and alcohols remain challenges for the future. Despite these improvements and benefits, these kinds of reagents have low atom efficiencies in that only the CF_3 group is used during reactions.

1.1.2.3 Radical Trifluoromethylation[29]

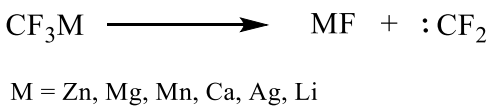
Radical trifluoromethylation is the oldest method for the synthesis of trifluoromethyl-containing organic molecules. Among the trifluoromethyl radical precursors, trifluoromethyl iodide,[41] trifluoromethyl bromide,[42] bis(trifluoromethyl) mercury,[43] silver trifluoroacetate,[44] the combination of sodium trifluoromethanesulfinate with tertiary butyl hydroperoxide,[45] and bis(trifluoroacetyl) peroxide[46] have been widely used for the trifluoromethylation of organic molecules (**Scheme 1-3**).[19] But some of these methods are not convenient processes, while other trifluoromethyl radical precursors are not readily available. Meanwhile, few examples have addressed the need for enantioselective radical trifluoromethylation reactions to date.[47]



Scheme 1-3. *Sources of trifluoromethyl radicals.* [19,29,41-46]

1.1.2.4 Nucleophilic Trifluoromethylation

The most popular and widely applied strategy of trifluoromethylation reactions is using the trifluoromethyl anion (CF_3^-) to introduce a CF_3 group into organic molecules.[20] Historically, one of the first concepts accessed the use of MCF_3-type reagents. However, trifluoromethyl magnesium reagents, including longer chain perfluoroalkyl magnesium reagents are more difficult to prepare than common alkyl magnesium reagents.[48] Moreover, CF_3^- is extremely unstable whereby the α-elimination of fluoride will generate difluorocarbene (CF_2:).[49] Ishikawa *et al*. and Wakselman *et al*. used CF_3ZnX (X = I, Br) reagents that were formed *in situ* to trifluoromethylate carbonyl compounds in poor yield.[50-51] Trifluoromethyl lithium and magnesium reagents cannot be used for nucleophilic trifluoromethylation, because metal fluoride is easily formed from the α-fluoride elimination reaction (**Scheme 1-4**).



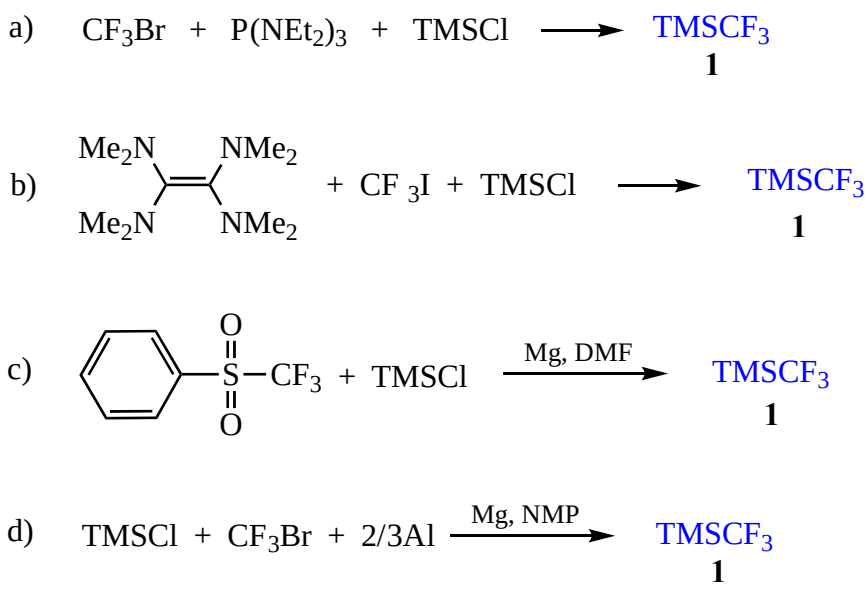
Scheme 1-4. *α-Elimination of metal fluoride.*[50-51]

It was found that transition metals or semi-metals (e.g., Sn, Si, or B) can stabilized the trifluoromethyl anion.[48] The use of toxic tin reagents is not common in trifluoromethylation reactions. In 2008, work from Vicic's group opened the door with very recent advances in the metal (Cu and Pd) mediated or catalyzed trifluoromethylations with trifluoromethyltrimethylsilane ($TMSCF_3$, Ruppert-Prakash reagent) on aryl halides, aryl and heteroaryl boronic acids, heteroarenes, indoles, vinyl sulfonates, active alkenes, and terminal alkynes.[52] These represent the first thermally stable and well defined ligand-

transition metal-CF_3 complexes. The compound $TMSCF_3$ was first prepared by Ruppert in 1984,[53] but it only received considerable attention after the discovery of its application of in the nucleophilic trifluoromethylation of carbon electrophiles in 1989 by Prakash and Olah.[54] Since then, $TMSCF_3$ has become the most popular reagent for the nucleophilic trifluoromethylation of organic compounds in the presence of an initiator, such as fluoride anion (CsF, TBAF, TBAT), alkoxide (*t*-BuOK), amine *N*-oxide (Me_3NO), acetate (LiOAc), *N*-heterocyclic carbenes (NHC), phosphine [P(*t*-Bu)$_3$], as well as electrophilic initiators such as Lewis acids (TiF_4/DMF, $Cu(OAc)_2$/dppe/toluene).[20] $TMSCF_3$ is the most understood and investigated of all of the trifluoromethylation reagents, and it has been used with suitable activators to introduce CF_3-groups into many carbon electrophiles, such as aldehydes, ketones, lactoles, lactones, carbonyl chlorides, carboxylic acid methyl esters, amides, *N*-aryl nitrones, and azirines. Recently, very significant research progress has been reported in metal (Cu and Pd) mediated or catalyzed trifluoromethylations using the Ruppert-Prakash reagent as a trifluoromethyl source.[13,55-56] In more than 350 publications since 2008, researchers have started their trifluoromethylation studies with $TMSCF_3$.[15]

Originally, $TMSCF_3$ was prepared from the reaction of bromotrifluoromethane (CF_3Br) and chlorotrimethylsilane (TMSCl) mediated by $(Et_2N)_3P$ via a bromophilic attack to transfer CF_3Br onto the silicon center of TMSCl (**Scheme 1-5**, Path a).[53] $TMSCF_3$ is a colorless liquid (b.p. 54-55 °C) that displays reasonable stability under acidic and non-anhydrous conditions. Commercially available $TMSCF_3$ **1** is primarily prepared using a modification of Ruppert's procedure in which anhydrous benzonitrile is used as solvent under a nitrogen atmosphere at -30 to -80 °C.[57] Other synthetic routes have been reported

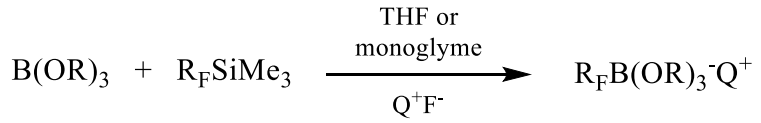
for obtaining **1** often via the development of nucleophilic trifluoromethylation reagents. For example, Pawelke reported that the low-temperature reaction of TMSCl with CF_3I in the presence of tetrakis(dimethylamino)ethylene gave **1** in 94% yield (**Scheme 1-5**, Path b).[58] The key for this reaction is to pre-generate the charge-transfer complex, which then acts as a nucleophilic trifluoromethylating agent and further transfers the CF_3-group to the silicon center when Me_3SiCl is applied. Prakash and coworkers prepared compound **1** in 45-83% yield via the magnesium metal-mediated reductive trifluoromethylation of TMSCl with the trifluoromethyl source phenyl trifluoromethyl sulfone in *N*,*N*-dimethyl-formamide (DMF) at 0 °C (**Scheme 1-5**, Path c).[59] Grobe and coworker reported that the reaction to generate **1** could be accomplished in an autoclave charged with TMSCl and CF_3Br in *N*-methyl-2-pyrrolidone (NMP) together with a stoichiometric amount of Al power at 50 °C (**Scheme 1-5**, Path d, 62% yield).[60]



Scheme 1-5. *Synthetic methods for $TMSCF_3$.* [53-60]

Today the Ruppert-Prakash reagent is widely used in both academics and industry for the preparation of CF_3-containing organic compounds. Trifluoromethylated boron reagents are also used for trifluoromethylation reactions, such as potassium (trifluoromethyl)trimethoxyborate [$CF_3B(OMe)_3^-K^+$].

In 2003, Röschenthaler and Molander *et al*. used the Ruppert-Prakash reagent with a trialkoxyborate [$B(OMe)_3$] and fluoride base to synthesize $CF_3B(OMe)_3^-K^+$ in excellent yields (**Scheme 1-6**).[61-62] Treatment of $TMSCF_3$ with fluoride gives the trifluoromethyl group, which is absorbed by the boron reagent to give the corresponding trifluoromethyl-containing borate salt. Crystalline potassium (trifluoromethyl)trimethoxyborate is moisture and air stable and can be used as a single component trifluoromethylation reagent. Dilman *et al*.[63] reported the utilization of potassium (trifluoromethyl)trimethoxyborate with carbonyl compounds and imines to synthesize trifluoromethylated alcohols and amines. Gooßen *et al*. also reported a one component trifluoromethylation of carbonyl compounds with $CF_3B(OMe)_3^-K^+$.[64]



R = Me, Et
R_F = CF_3, C_2F_5, $(EtO)_2P(O)CF_2$
Q^+ = K^+, Me_4N^+

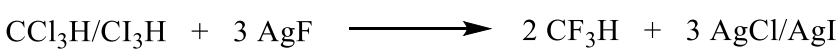
Scheme 1-6. *Synthesis of perfluoroalkyltrifluoroborates.*[61-62]

However, the nucleophilic trifluoromethylation reactions have an unclear prospect from the limited production and increasing cost of the CF_3^- source. The common methods to synthesize $TMSCF_3$ start from trifluoromethyl halides, such as CF_3Br and CF_3I.

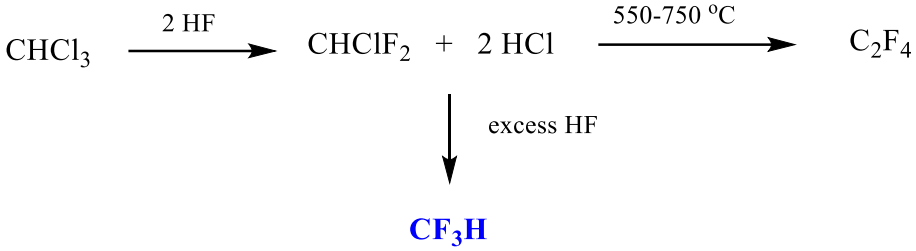
Trifluoromethyl halides have been claimed as ozone-depleting gases. The price of $TMSCF_3$ has increased because such trifluoromethyl halides are now banned by the Montreal Protocol. Therefore, the development of new synthetic routes to $TMSCF_3$ or other stable CF_3-containing building blocks starting from an environmentally friendly and economically efficient, alternative source of the trifluoromethyl group is highly desirable.

1.1.3 Trifluoromethylation Based on Fluoroform

The best solution for this problem is the use of fluoroform (trifluoromethane, HFC-23; CF_3H, MW = 70.0; CAS number 75-46-7; pK_a = 25-28 in water) as the source of the trifluoromethyl group.[65] In 1890, Chabrié and Meslans reported the isolation of CF_3H. This last member of the haloform family was generated from the reactions of silver fluoride (AgF) with either chloroform (CCl_3H) or iodoform (CI_3H) (**Scheme 1-7**).[66] In 1937, Henne described the extreme chemical and physiological inertness of this compound; he also discovered the low toxicity of fluoroform by maintaining a guinea pig in an artificial atmosphere containing up to 80% CF_3H.[67] One year later, Plunkett made one of the most important discoveries of the 20th century at the DuPont Company.[68] He accidentally discovered the self-polymerization of tetrafluoroethylene (TFE), which gave the new polymer poly(tetrafluoroethylene) (PTFE, also now known under the Chemours trademark of Teflon®).[65] As shown in **Scheme 1-8**, 20,000$^+$ metric tons of CF_3H are generated



Scheme 1-7. *Chabrié and Meslans's synthesis of CF_3H.*[66]

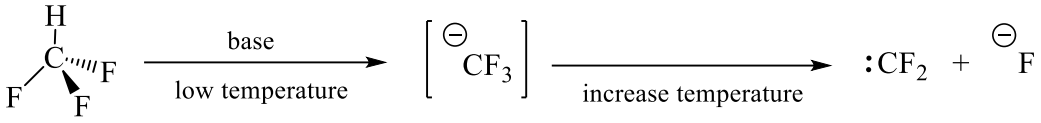


Scheme 1-8. *Generation of CF_3H as the by-product during the production of PTFE.*[65]

annually as a by-product from the manufacture of tetrafluoroethylene, the monomer of PTFE. Furthermore, fluoroform has been largely produced as a byproduct during the industrial preparation of other fluorinated refrigerants and polymers. No industrial application of such an inert material as CF_3H exists, and thus, it is projected that about 24,300 metric tons of CF_3H had been released into the atmosphere by 2015.

However, this chemically inert, non-flammable, nontoxic, and ozone friendly compound is of serious concern due to its formidable global warming potential, which is 11,700 times greater than that of CO_2 on a per molecule basis, as its atmospheric lifetime is more than 250 years.[69] A common solution is to treat CF_3H as a chemical waste. But then high-energy consumption is required to burn CF_3H, and special materials are required to bear the 1200 °C required for the former as well as to absorb the generated HF. Large amounts of environmentally unfriendly inorganic fluorides are generated during the neutralization of the HF formed in this process.[70] All of the aforementioned problems force the formation of an important target in fluorine chemistry, namely the transformation of CF_3H into valuable fluorochemicals. Meanwhile, the solution of this target will give a very cheap and abundant source of CF_3 groups. However, such a transformation is challenging. The compound CF_3H is a gas (boiling point -82 °C) and a weak C-H acid (pK_a = 25-28 in

water), and the lack of reactive sites on the molecule makes it kinetically inert. Only strong bases can deprotonate CF_3H to generate the highly unstable trifluoromethyl anion (CF_3^-). Furthermore, the CF_3^- anion is easily decomposed to form fluoride anion (F^-) and singlet difluorocarbene ($:CF_2$) (**Scheme 1-9**).

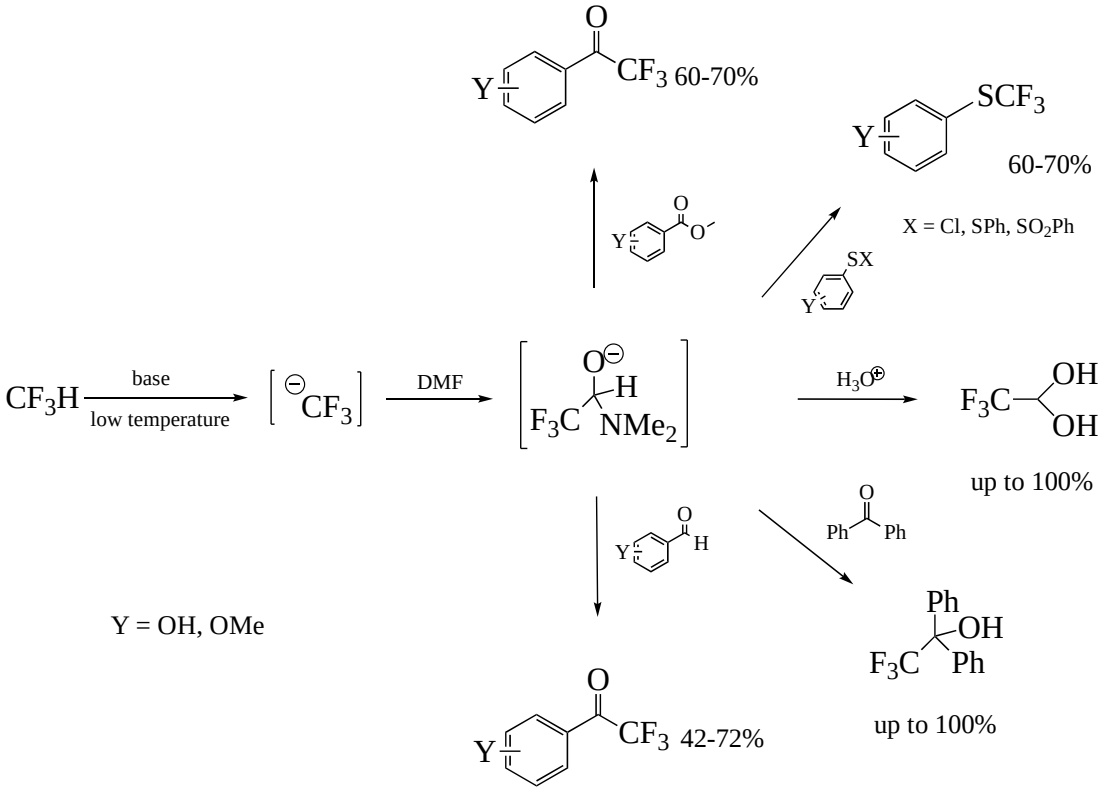


Scheme 1-9. *Decomposition of trifluoromethyl anion generated from CF_3H.*

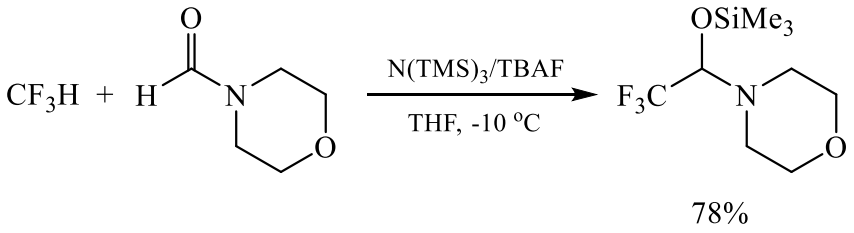
In 1991, Shono and coworker reported the first successful attempt to use CF_3H as a trifluoromethylation source. Fluoroform was deprotonated with a strong base, such as *t*-BuOK or NaH, in dimethylformamide (DMF) to give the CF_3^- equivalent product. This CF_3^- equivalent reacted with aldehydes to give the corresponding trifluoromethylated secondary alcohols in low to moderate yields.[71] The yields of trifluoromethylated secondary alcohols were improved to 92% yield when electrochemically generated 2-pyrrolidonide was used as the base in the presence of hexamethyldisilazane (HMDS). After that, Troupel *et al*. reported the preparation of the CF_3-containing secondary alcohols in 12-76% yields from the reaction of aldehydes with the CF_3^- equivalent formed by the electrochemical deprotonation of CF_3H in DMF.[72] Moreover, the research groups of Russell, Normant, and Langlois also successfully developed the trifluoromethylation of organic compounds using the CF_3^- equivalent generated from CF_3H (**Scheme 1-10**).[73-77]

In 2000, Langlois *et al*. synthesized a new nucleophilic trifluoromethylation reagent from fluoroform. The anion CF_3^- was generated via the deprotonation of CF_3H with tris(trimethylsilyl)amine [$N(TMS)_3$] and tetra-*n*-butylammonium fluoride (TBAF) in THF

and was then trapped by *N*-formylmorpholine to form the stable Langlois reagent (**Scheme 1-11**).[78] Unfortunately, no further applications of this reagent were reported because of its lower reactivity compared to the Ruppert-Prakash reagent.[79]



Scheme 1-10. *Trifluoromethylation of carbonyl and sulfur electrophiles with CF_3H/base in DMF.*[73-77]

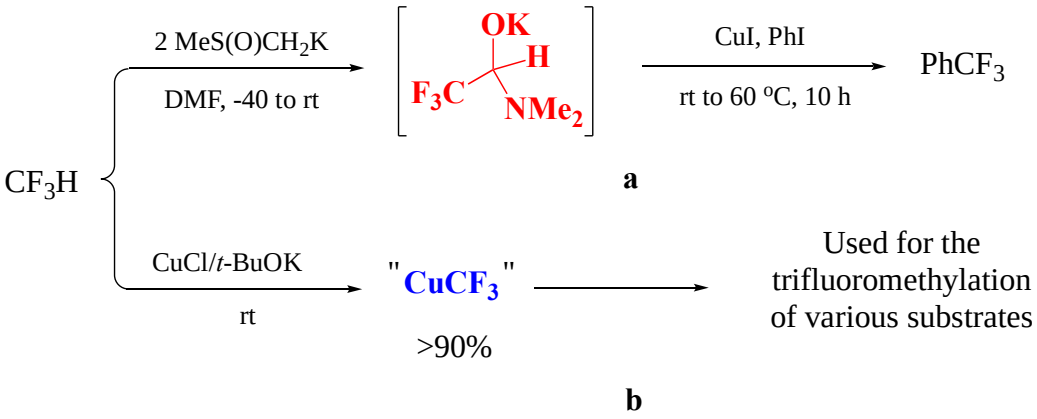


Scheme 1-11. *Synthesis of Langlois reagent.*[78]

1.1.4 Recent Developments in Trifluoromethylation and Difluoromethylation Chemistry Based upon Fluoroform

Since the direct synthesis of potassium (trifluoromethyl)trimethoxyborate from fluoroform was initially investigated, it was interest to us that several research groups have focused on the development of new methods for the usage of CF_3H as a source of trifluoromethyl groups for trifluoromethylation and difluoromethylation.[80] These recent research results will be briefly discussed herein.

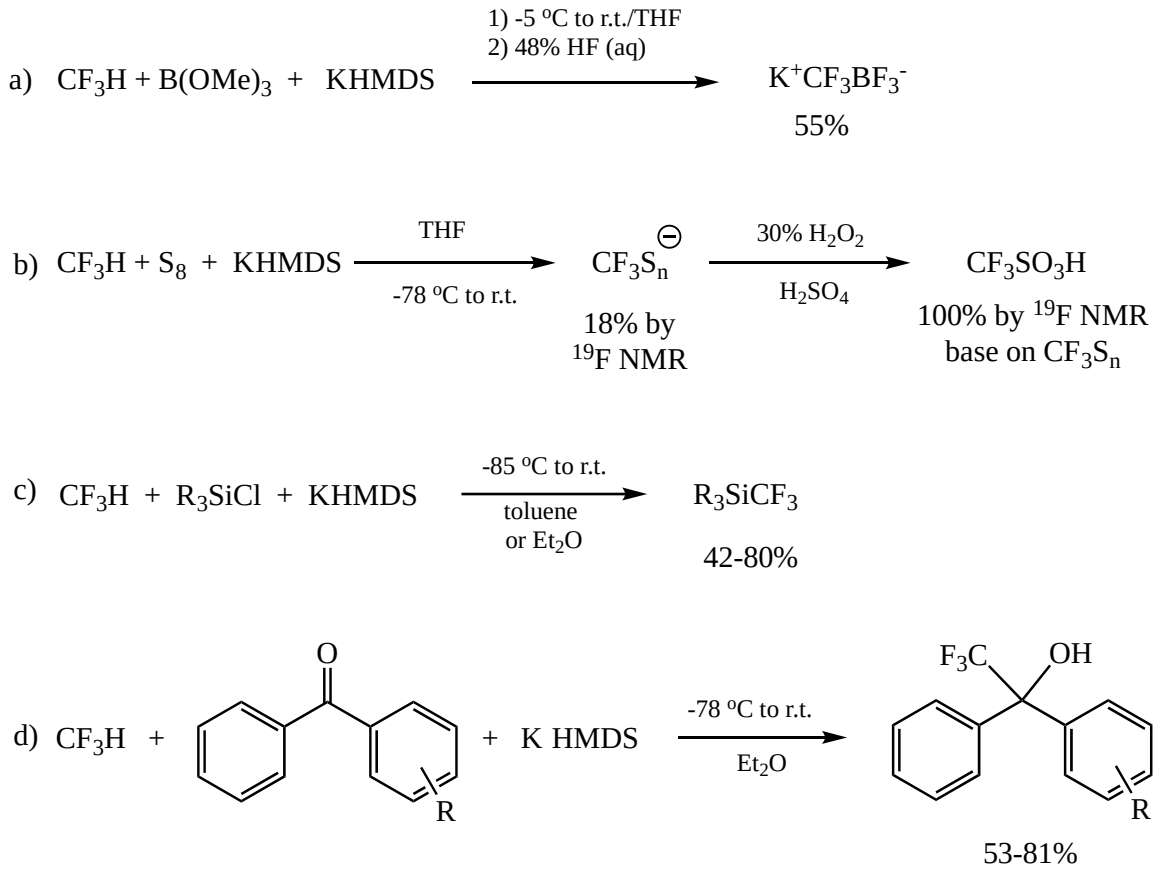
In 2011, Grushin *et al.* first reported the introduction of the trifluoromethyl group into organic molecules using fluoroform as the most attractive CF_3 source.[81] As shown in Path a of **Scheme 1-12**, the stable potassium hemiaminolate intermediate was detected by NMR spectroscopy in the reaction of a copper-mediated trifluoromethylation of haloarenes using CF_3H with $MeS(O)CH_2K$ (Dimsyl-K) in DMF. Furthermore, the reaction of CuCl and *t*-BuOK (1:2) in DMF gave *in situ* the corresponding alkoxycuprate, which readily reacted with CF_3H (at room temperature and 1 atm) to provide $CuCF_3$ for further reaction with a variety of substrates as shown in **Scheme 1-12**, Path b. The $CuCF_3$ species was



Scheme 1-12. *Grushin's synthesis of $CuCF_3$ by cupration of CF_3H.*[81]

efficiently stabilized with hydrogen fluoride triethylamine (TREAT-HF) to form $CuCF_3$ reagents that readily trifluoromethylated various organic substrates, such as aryl, heteroaryl halides, α-halo ketones, and aryl boronates. Rozen *et al*. utilized this $CuCF_3$ reagent for the synthesis of trifluoromethylated thiocyanates.[82]

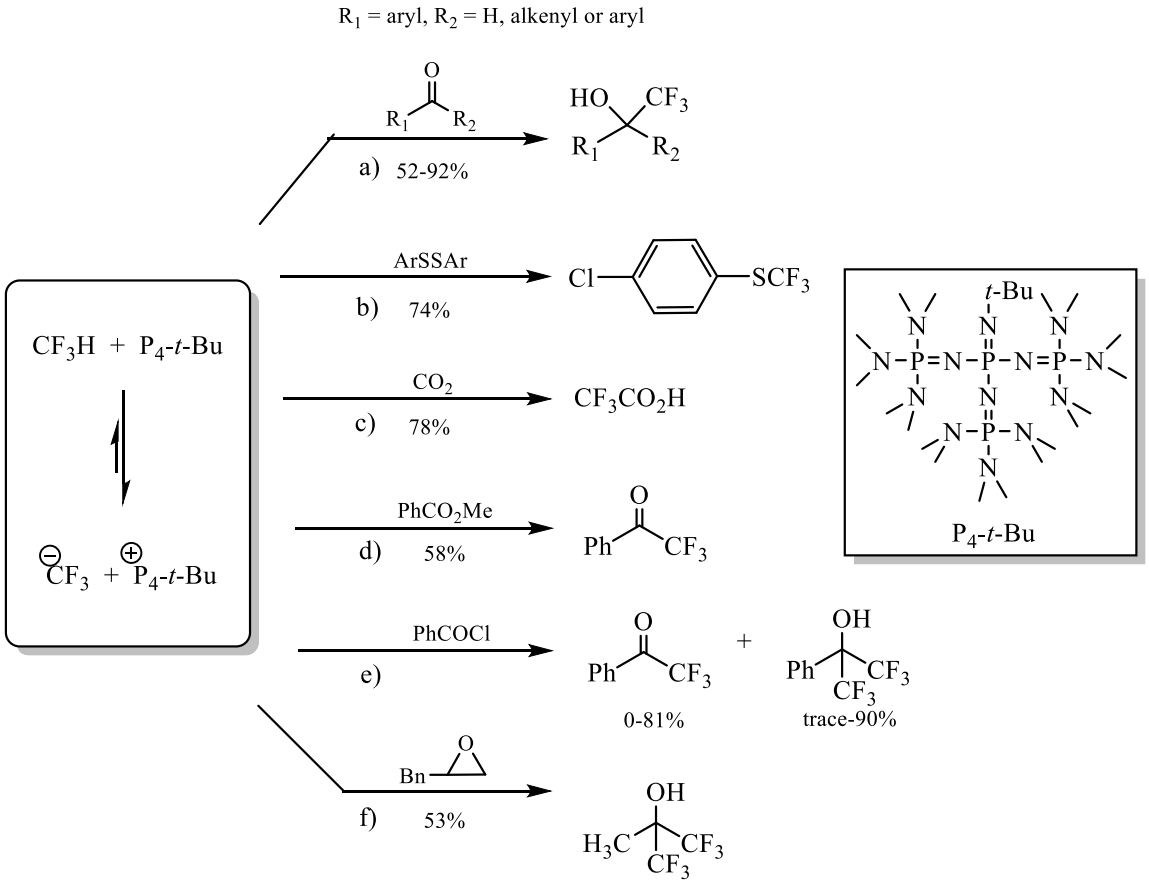
Moreover, Prakash *et al*. reported the synthesis of common and widely studied trifluoromethylation reagents through the deprotonation of CF_3H with potassium bis(trimethylsilyl)amide (KHMDS) in ethereal solvents.[83] For example, potassium (trifluoromethyl)trifluoroborate ($CF_3BF_3^-K^+$), trifluoromethane sulfonic acid, and trialkyl trifluoromethylsilanes were all prepared (**Scheme 1-13**, Paths a-c). This method can also



Scheme 1-13. *Direct trifluoromethylation using CF_3H with KHMDS.*[83]

be used for the nucleophilic trifluoromethylation of non-enolizable ketones, esters, chalcones, and formate esters (**Scheme 1-13**, Path d). My research on trifluoromethylation with CF_3H is similar to Prakash's work and will be discussed later.

Meanwhile, in 2013 Shibata *et al*. reported the addition of the trifluoromethyl group to ketones with fluoroform in the presence of the organic super base, 1-tert-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)-phosphoranylidenamino]-2λ^5,4λ^5-catena di(phosphazene) (P_4-*t*-Bu) (**Scheme 1-14**, Paths a-b).[84] The CF_3 anion was generated at -30 °C using THF as solvent. Nucleophilic trifluoromethylation using CF_3H in the presence of P_4-*t*-Bu was further developed by Mikami *et al*. The direct trifluoromethylation with

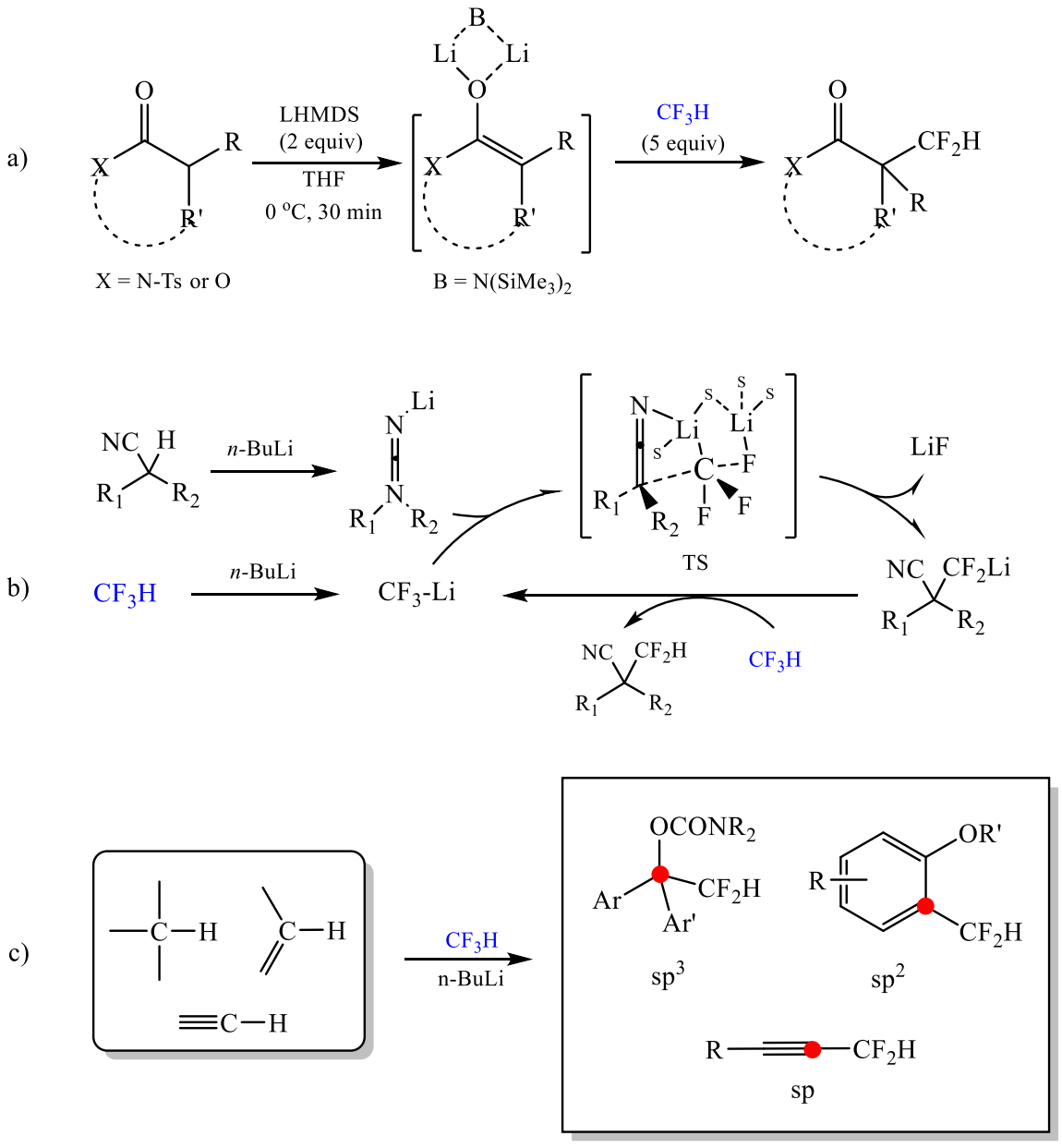


Scheme 1-14. *Direct trifluoromethylation using CF_3H in the presence of P_4-4-Bu.*[84-85]

CF_3H in the presence of this special super base is achieved on various organic compounds including acid chlorides, esters, carbon dioxide, and epoxides (**Scheme 1-14**, Paths c-e).[85] Interestingly, the reaction with a terminal epoxide occurs at the more hindered carbon atom to give the corresponding tertiary alcohol (**Scheme 1-14**, Path f).

In 2012, Mikami and co-workers described the first example of direct difluoromethylation by a polarity-inversion approach on the generated trifluoromethyl carbanion, i.e., an umpolung of fluoroform by activation of an inert C-F bond to form a difluoromethyl carbocation equivalent.[86] Lithium hexamethyldisilazide (LHMDS) is the key reagent for the formation of α-difluoromethyl products. Substrates did not capture difluoromethyl carbene under the reaction condition. The activation of the C-F bond of CF_3H through the strong Li···F interaction with the lithium enolate that was generated *in situ* gave directly the difluoromethyl product (**Scheme 1-15**, Path a). However, only lactones and lactam enolates were effective for this difluoromethylation method. In 2015 and 2016, Mikami *et al*. have achieved the difluoromethylation of the sp^3 carbon atom of various nitriles, the sp^3 carbon atom of alkanes, the sp^2 carbon atom of arenes, and the sp carbon atom of alkynes with CF_3H using *n*-butyllithium (*n*-BuLi) as the base (**Scheme 1-15**, Paths b-c).[87-88]

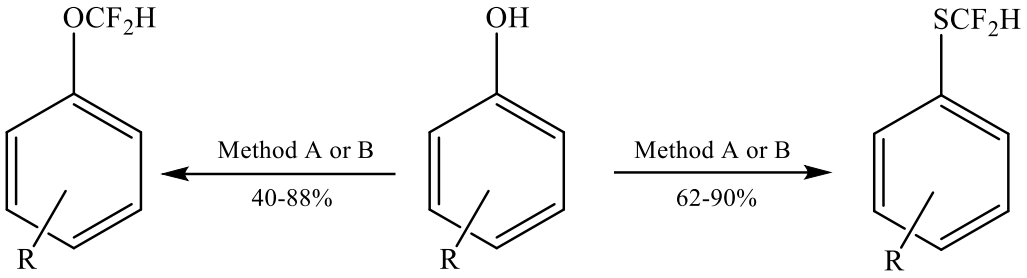
In 2013, Dolbier *et al*. reported that fluoroform could be used as a source of difluorocarbene in the presence of NaOH or KOH. The novelty of this reaction is the deprotonation of CF_3H with the formation of the trifluoromethyl anion when using more common inorganic bases. The reaction of phenols and thiophenols with the difluorocarbene



Scheme 1-15. *Difluoromethylation using CF_3H and Li base.*[86-88]

that was generated *in situ* from α-fluoride elimination from the CF_3^- anion at high temperature gave the corresponding difluoromethyl ethers and thioethers **(Scheme 1-16)**.[89]

In 2014, Prakash, *et al*. reported the capture and study of a long-lived trifluoromethanide anion from reactions involving both fluoroform and the Ruppert-



Method A: CF_3H (8 equiv), KOH (10 equiv), H_2O/dixane, 50 ^oC
Method B: CF_3H (14.2 equiv), KOH (15 equiv), H_2O/MeCN, r.t., 50 ^oC

Scheme 1-16. *Difluoromethylation using CF_3H with KOH.*[89]

Prakash reagent. To stabilize the trifluoromethanide, the anion was paired with a potassium cation and a crown ether (18-crown-6) to generate the corresponding potassium crown ether complex. Then the existence of a long-lived trifluoromethanide anion was confirmed by low-temperature NMR spectroscopy.[90]

In comparison, trifluoromethylations using $CuCF_3$ generated from fluoroform are not one-pot syntheses, and the Cu species produced as by-products represent a heavy metal pollutants. Meanwhile, Prakash's and Shibata's direct trifluoromethylation approaches that start with the deprotonation of CF_3H require very expensive super bases such as KHMDS and P_4-*t*-Bu, respectively. And Dolbier's difluoromethylation methodology to prepare difluoromethyl ethers and thioethers requires large excess amounts of inorganic base (10 to 15 equiv. of KOH).

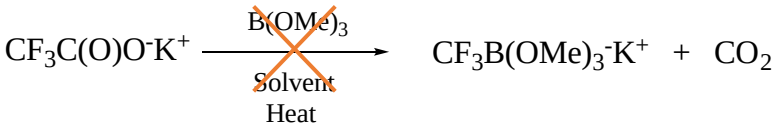
During the 253rd ACS National Meeting & Exposition in San Francisco, CA in April 2017, Geri and Szymczak disclosed results that are very similar to my research in that sodium or potassium dimsyl was used to deprotonate fluoroform for the preparations of nucleophilic, radical, and electrophilic trifluoromethylation reagents.[91-92]

1.2 Results and Discussion

The purpose of the research reported herein was to explore a new, inexpensive, and green method for the preparation of widely-used nucleophilic trifluoromethylation reagents. Furthermore, it was hoped that the methods developed might eventually be used by other scientists both in academics and industry.

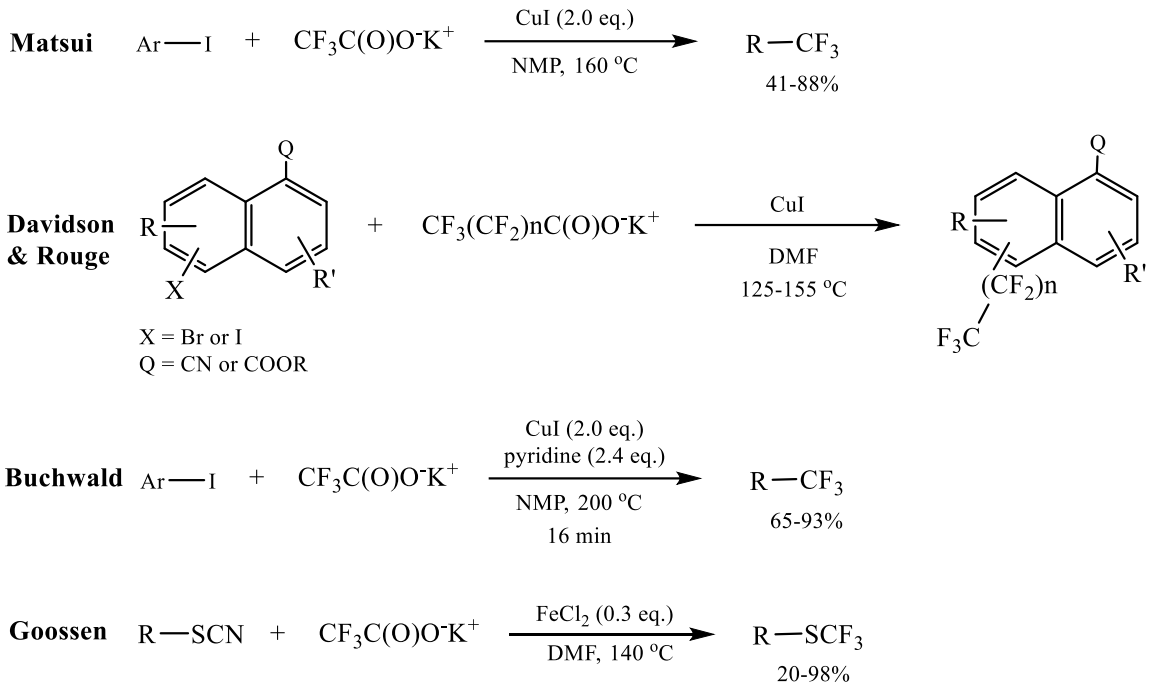
1.2.1 Attempted Synthesis of $CF_3B(OMe)_3^-K^+$ using Potassium Trifluoroacetate as a Trifluoromethyl Source

The moisture and air stable, crystalline potassium (trifluoromethyl)-trimethoxyborate [$CF_3B(OMe)_3^-K^+$] has been previously used as a nucleophilic trifluoromethylation reagent.[62] The salt $CF_3B(OMe)_3^-K^+$ was originally prepared using $TMSCF_3$ as the trifluoromethyl source (**Scheme 1-6**).[61-62] Due to the limited production and increasing price of $TMSCF_3$, we initially planned a one-step reaction to synthesize $CF_3B(OMe)_3^-K^+$ **2** from the decarboxylation of potassium trifluoroacetate [$CF_3C(O)O^-K^+$] (**Scheme 1-17**). Metal trifluoroacetates are readily available and a cheap source of trifluoromethyl groups. In 1981, Matsui *et al*. claimed a convenient trifluoromethylation of aromatic halides via the decarboxylation of sodium trifluoroacetate in the presence of copper(I) iodide at 140 °C.[93] In 1985, Davidson and Rouge improved this method by using



Scheme 1-17. *Attempted preparation of $CF_3B(OMe)_3^-K^+$ from $CF_3C(O)O^-K^+$.*

potassium perfluoroalkanoates for preparing perfluoroalkylaromatic compounds at 125 to 155 °C.[94] In 2013, Buchwald described an effective trifluoromethylation of aromatic and heteroaromatic iodides using $CF_3C(O)O^-K^+$ with CuI in a flow system.[95] Later, Gooßen reported the application of an iron-catalyzed decarboxylation of $CF_3C(O)O^-K^+$ for the synthesis of trifluoromethyl thioethers (**Scheme 1-18**).[96]



Scheme 1-18. *Examples of using metal perfluoroalkanoates as sources of perfluoroalkyl groups.*[93-96]

In the current work, a mixture of $CF_3C(O)O^-K^+$ and trimethyl borate was heated in a polar organic solvent under inert atmosphere in an effort to start the decarboxylation. Polar aprotic solvents were used to dissolve the $CF_3C(O)O^-K^+$. As the reaction conditions shown in **Table 1-2** indicate, DMF was used as the solvent for entries 1 to 6. Tetrahydrofuran (THF) was also used as the solvent (entry 7). The molar ratio of reactants,

reaction temperature, and reaction time were all screened, but all these reactions failed to give the desired compound **2** (entries 1 to 7).

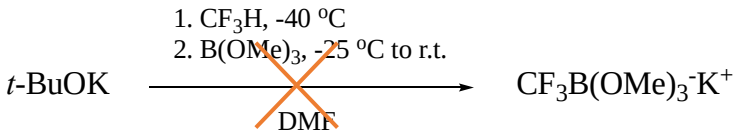
As decarboxylation reaction normally requires high reaction temperature, it is thought that the potassium (trifluoromethyl)trimethoxyborate [$CF_3B(OMe)_3^-K^+$] **2** would be unstable at such reaction temperatures. To investigate the thermal stability of compound **2**, a sample of **2** was prepared from $TMSCF_3$ by the published procedures.[61-62] As expected, a ^{19}F NMR spectroscopic study showed that compound **2** decomposes at 80 °C. When the reaction was carried out at lower temperature, no reaction was observed (entries 4-5). In addition, the reaction was studied under ultrasonic conditions, but the desired compound **2** was also not formed. Therefore, it appears not to be possible to prepare compound **2** from the decarboxylation of metal trifluoroacetates, at least under the conditions tried.

Table 1-2. *Preparation of $CF_3B(OMe)_3^-K^+$ from $CF_3C(O)O^-K^+$*

	$CF_3C(O)O^-K^+$ (eq.)	$B(OMe)_3$ (eq.)	Temperature (°C)	Solvent	Time (h)	$CF_3B(OMe)_3^-K^+$
1	1	1	130	DMF	3	-
2	1	1.5	105	DMF	48	-
3	1	1.5	150	DMF	12	-
4	1	1.5	90	DMF	2.5	-
5	1	1.5	60	DMF	2	-
6	1	1.5	r.t. (Ultrasonic)	DMF	0.5	-
7	1	1.5	r.t. (Ultrasonic)	THF	0.5	-

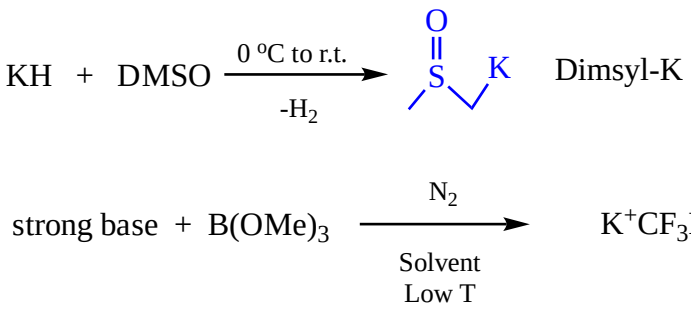
1.2.2 Synthesis of $CF_3B(OMe)_3^-K^+$ using Fluoroform as a Trifluoromethyl Source

As was stated in the Introduction, fluoroform has been proven as an abundant and cheap trifluoromethyl source for trifluoromethylation. However, the synthesis of $CF_3B(OMe)_3^-K^+$ and $TMSCF_3$ using CF_3H as the trifluoromethyl source had not yet been reported when I began my Ph.D. studies on this topic. Hence, CF_3H was used as an alternative trifluoromethyl group source for the synthesis of the compound $CF_3B(OMe)_3^-K^+$. As shown in **Scheme 1-19**, when DMF was used as solvent, treatment of CF_3H with *t*-BuOK at -40 °C followed by addition of $B(OMe)_3$ failed to give the desired product $CF_3B(OMe)_3^-K^+$ **2**. This failure was due to the fact that the CF_3^- generated *in situ* by the deprotonation of CF_3H with *t*-BuOK was trapped by *N*,*N*-dimethylformamide (DMF) to give the stable trifluoromethylating hemiaminolate species,[81] and this species would not react with $B(OMe)_3$ to produce the desired compound **2**. Therefore, a solvent that can trap the *in situ* generated CF_3^- should not be used for preparation of compound **2**.



Scheme 1-19. *Attempted preparation of $CF_3B(OMe)_3^-K^+$ using CF_3H in DMF.*

Then dimethyl sulfoxide (DMSO) or THF was used as the solvent for the preparation of $CF_3B(OMe)_3^-K^+$ **2**. Furthermore, the super strong base (dimsyl-K), first prepared by Corey in 1965 from a mixture of potassium hydride (KH) and dimethyl



Scheme 1-20. *Investigation of the formation of $K^+CF_3B(OMe)_3^-$ from CF_3H.*

sulfoxide (DMSO),[97] was used for the deprotonation of CF_3H (**Scheme 1-20**). As shown in **Table 1-3**, when the reaction proceeded at room temperature, compound **2** was not formed (**Table 1-3**, entry 1). To our delight, both the ^{19}F and ^{11}B NMR spectra of the reaction mixture showed that $CF_3B(OMe)_3^-K^+$ was formed when the reaction was carried out at -100 °C in the presence of two equivalents of $B(OMe)_3$ (**Table 1-3**, entry 3).

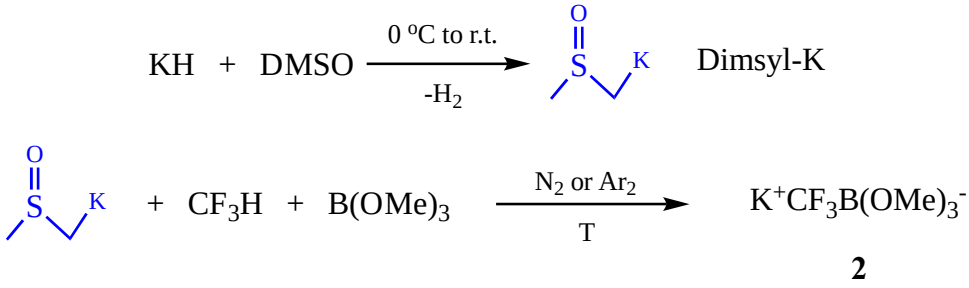
Table 1-3. *Investigation of the formation of $K^+CF_3B(OMe)_3^-$ from CF_3H*

	Base	$B(OMe)_3$	Solvent	Temperature (°C)	$KCF_3B(OMe)_3$
1	K-dimsyl	1	DMSO	r.t.	-
2	K-dimsyl	1	THF	-40	-
3	K-dimsyl	2	THF	-100	Found

Then we turned our attention to the optimization of the reaction conditions in order to improve the yield of $K^+CF_3B(OMe)_3^-$. As shown in **Table 1-4**, a very low reaction temperature (-75 to -94 °C) was found to be extremely important for the formation of compound **2**. In addition, it is necessary that the fluoroform be slowly bubbled into the

mixture of $B(OMe)_3$ with K-dimsyl in THF, which enables the unstable trifluoromethyl anion generated *in situ* to be quenched efficiently by $B(OMe)_3$ to form compound **2**.

Table 1-4. *Optimization of reaction conditions for the synthesis of $K^+CF_3B(OMe)_3^-$ from CF_3H*



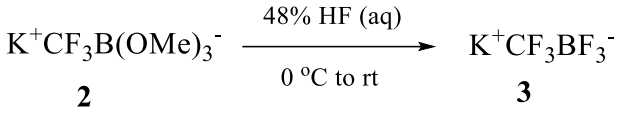
2

	K-dimsyl/$B(OMe)_3$	Temperature (°C)	Time (h)	Product **2** (%)*
1	1/1	-40	2	-
2	1/2	-90	1.5	trace
3	1/2	-25	2	-
4	1/2	-60	3	-
5	1/2	-90	4	85
6	1/2	-94	12	51
7	1/2	-75	2	88

*Yield was determined by ^{11}B NMR spectral analysis

Although CF_3H was converted into $K^+CF_3B(OMe)_3^-$ **2** at the optimized reaction conditions in high yield **(**88% yield as determined by the ^{11}B and ^{19}F NMR spectra, **Table 1-4**, entry 7), it was difficult to isolate the salt from reaction mixture. Compound **2** seems to be unstable under the reaction conditions. It was found that compound **2** decomposed and finally disappeared when the reaction time was extended. Hence,

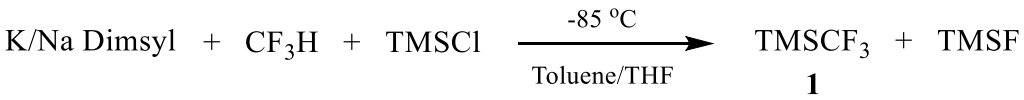
$K^+CF_3B(OMe)_3^-$ **2** was smoothly fluorinated by 48% HF (aq) to give the more stable $K^+CF_3BF_3^-$ **3** (**Scheme 1-21**).[62]



Scheme 1-21. *Synthesis of $K^+CF_3BF_3^-$.*[62]

1.2.3 Synthesis of $TMSCF_3$ using Fluoroform as a Trifluoromethyl Source

During my research on direct trifluoromethylation using fluoroform as a source of the trifluoromethyl group, similar reactions were reported by Prakash's group (**Scheme 1-13**).[83] But a significant difference exists between our reaction and Prakash's method. Potassium bis(trimethylsilyl)amide was used as the base by Prakash and coworkers. We used the much cheaper base dimsyl-K that was prepared from potassium hydride (KH) and DMSO. The preparation of the nucleophilic trifluoromethylation reagent $TMSCF_3$ **1** from the reaction of TMSCl with the CF_3^- anion generated *in situ* by deprotonation of CF_3H with M-dimsyl (M = Na or K) was carried out for 2 hours at -85 °C (**Scheme 1-22**). The ^{19}F NMR spectrum of the reaction mixture showed that the desired compound **1** was successfully formed along with a large amount of fluorotrimethylsilane



Scheme 1-22. *Attempted preparation of $TMSCF_3$ using CF_3H.*

(TMSF) in an initial experiment at -85 ˚C. To improve the yield of $TMSCF_3$ **1**, a number of reaction conditions was investigated. When the reaction time was increased from 2 to 4 h at -80 °C, the formation of TMSF was inhibited, but the desired compound $TMSCF_3$ was formed in low yield **(Figure 1-4)**. This may be due to the low solubility of K-dimsyl in THF and toluene, as a lot of suspended material was observed in the reaction mixture.

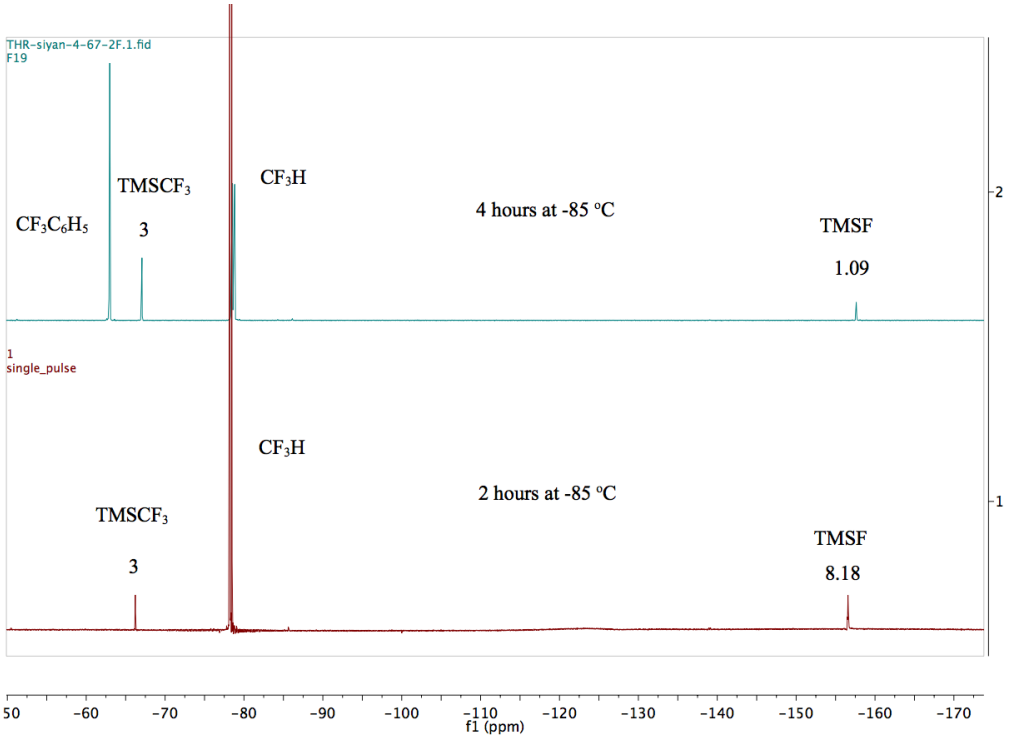
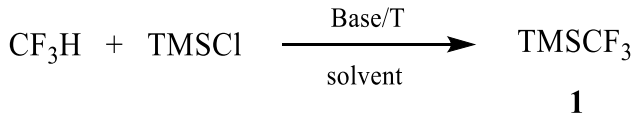


Figure 1-4. *The formation of TMSF was inhibited when the reaction time was extended at low temperature.*

Meanwhile, another cheaper super strong base, sodium methylsulfinylmethylide (Na-dimsyl), prepared from the reaction of sodium hydride (The NaH was pre-washed with hexane to remove the oil, and the resulting solid was dried under a flow of argon gas.) with DMSO at 75 °C for 1 h, was used as the base for the same reaction. Unfortunately, $TMSCF_3$ was not formed using Na-dimsyl as the base.

Recently, Dolbier *et al*. described the reaction of phenols and thiophenols with difluorocarbene generated *in situ* from the CF_3^- anion that was formed from CF_3H in the presence of NaOH or KOH.[89] This result showed that the commercially available and cheap bases NaOH and KOH can deprotonate CF_3H. Accordingly, KOH was used as base for preparation of $TMSCF_3$ from CF_3H. However, as shown in **Table 1-5**, no reaction occurred when the reaction mixture was stirred at -20 or -40 °C (entries 1-2). As KOH has extremely low solubility in THF, a crown ether (18-crown-6) was added to chelate the potassium cation for improvement of the solubility, and still no reaction was observed when THF was used as solvent (entry 3). Interestingly, when dioxane was used as solvent instead of THF, the ^{19}F NMR spectrum of the reaction mixture (**Figure 1-5**) showed that the desired compound $TMSCF_3$ was not formed, but a fluorine-containing compound was produced in very low yield (**Table 1-5**, entry 5). As a doublet resonance at -86 ppm was observed for this compound (**Figure 1-5**), it may be the difluoromethyloxy-containing compound.

Table 1-5. *Attempted synthesis of $TMSCF_3$ from CF_3H using KOH as base*



1

Entry	Base	Temperature (°C)	Solvent	Result
1	KOH	-20	THF	No reaction
2	KOH	-40	THF	No reaction
3	KOH/18-crown-6	-20	THF	No reaction
4	KOH/18-crown-6	-5	THF	No reaction
5	KOH/18-crown-6	-5	dioxane	Reacted

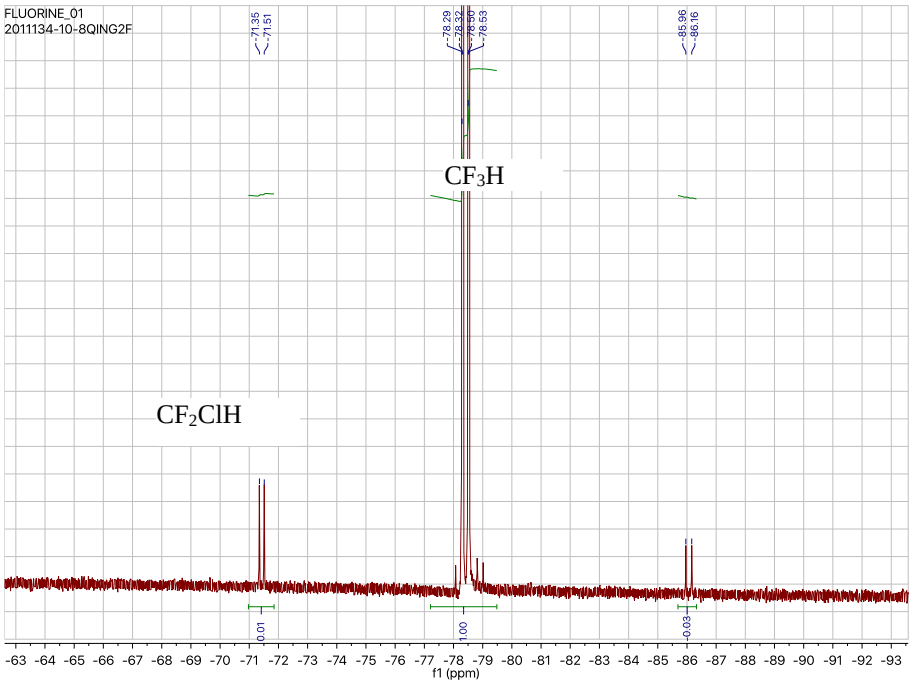
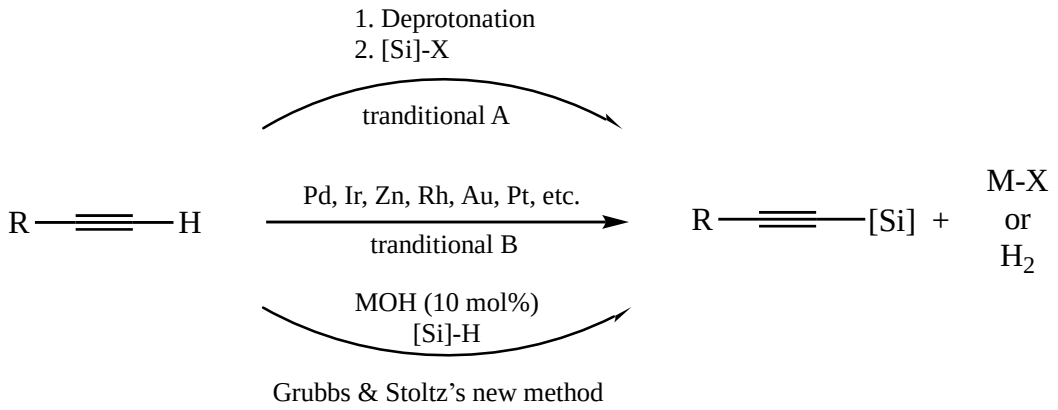


Figure 1-5. *^{19}F NMR spectrum of trifluoromethylation from CF_3H using KOH as base.*

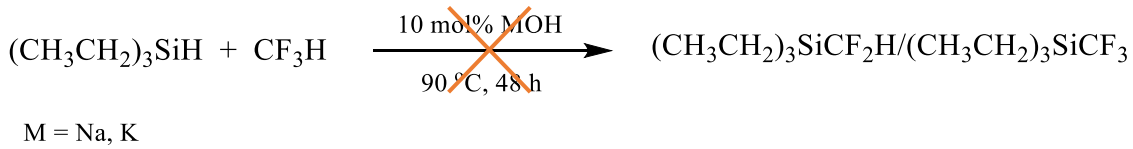
1.2.4 Attempted Synthesis of $TMSCF_3$ from CF_3H via a C-H Bond Silylation Catalyzed by an Alkali Metal-hydroxide

Very recently, Stoltz and Grubbs reported the alkali hydroxide-catalyzed direct silylation of C-H bonds in terminal alkynes and aromatic heterocycles (**Scheme 1-23**), where either stoichiometric or catalytic amounts of transition metals were used to deprotonate terminal alkynes.[98-99] Therefore, both the NaOH- and KOH-catalyzed silylations of CF_3H for the synthesis of R_3SiCF_3 were attempted. A mixture of triethylsilane [$(CH_3CH_2)_3SiH$], fluoroform (CF_3H), and 10 mol% of either NaOH or KOH was stirred in



Scheme 1-23. *Grubbs & Stoltz's C-H bond silylation catalyzed by an alkali metal-hydroxide.*[98-99]

a sealed glass tube under an argon atmosphere at 90 °C for 48 h (**Scheme 1-24**). Unfortunately, the ^{19}F NMR spectrum of the reaction mixture showed that CF_3H was not converted into any fluorine-containing compound.



Scheme 1-24. *Attempted KOH-catalyzed silylation of CF_3H.*

1.3 Summary

In conclusion, methods for the use of fluoroform (CF_3H) as a cheap and abundant trifluoromethyl source and potassium dimsyl as a base for the preparation of widely used nucleophilic trifluoromethylation reagents trifluoromethyltrimethylsilane ($TMSCF_3$) and potassium (trifluoromethyl)trimethoxyborate [$CF_3B(OMe)_3^-K^+$] have been successfully developed. The direct trifluoromethylation with CF_3H avoided the use of an ozone-

depleting reagent, such as CF_3Br and CF_3I. However, the low solubility of K-dimsyl in the solvents tested as well as the high melting points of those solutions have limited the potential application of this method to date. Perhaps an improved solvent system can be identified in the future. It should be noteworthy that in the 253rd ACS National Meeting & Exposition in San Francisco in April 2017, Geri and Szymczak reported a similar result that metal-dimsyl was used to deprotonate CF_3H for the preparations of nucleophilic, radical, and electrophilic trifluoromethylation reagents, but $TMSCF_3$ was not directly prepared from CF_3H by their procedures.[91-92]

1.4 Experimental Section

1.4.1 General Experimental Methods

1.4.1.1 Freeze-Pump-Thaw

A solvent in a closed flask is first frozen by immersion of the container in a Dewar of liquid nitrogen (N_2). While being maintained at -196 °C, a valve to the container is opened under high vacuum when attached to a vacuum line in order for the interior of the vessel to reach the best obtainable vacuum level while the solvent is completely frozen. The valve to the container is then closed, and its contents are warmed slowly until the solvent completely melts. This process is repeated three times and after the last cycle the container is filled with an inert anhydrous gas, such as nitrogen or argon.

1.4.1.2 Purging

Purging is a less effective way of degassing solvents than freeze-pump-thaw; however, it is acceptable in certain situations, particularly when a vacuum pump is not available and/or large amounts of solvent are required to be degassed. Inert gas (N_2 or Ar) is slowly bubbled through the solvent for a period of 0.5 to 1 hour. Both solvent evaporation and condensation of moisture in the solvent should be avoided during this process.

1.4.1.3 Drying Solvent over 3 Å Molecular Sieves

Synthesis including moisture sensitive conditions always requires anhydrous solvents. Common methods for drying solvents include the use of drying agents, refluxing with sodium wire in the presence of benzophenone as indicator, etc. Williams claimed that 3 Å molecular sieves can simply and significantly reduce the water content better than other methods in THF.[100] The residual water content in THF is 43.4 ppm after 48 h reflux with Na/benzophenone, while the amount of moisture is only 6.1 ppm with 3 Å molecular sieves, as measured by Karl Fischer titration. Molecular sieves (3 Å) were used to dry toluene (0.9 ppm, 24 h), dichloromethane (0.1 ppm, 24 h), acetonitrile (0.5 ppm, 24 h), and lower alcohols. Activation or regeneration is required to remove the moisture from the molecular sieves. The molecular sieves (3 Å) are heated to 175-260 °C overnight in a vacuum oven, and then they are slowly cooled to room temperature and stored in a sealed

container for future usage. All solvents are dried with 3 Å molecular sieves for at least 24 h, and a Karl Fischer titrator is used to measure the residual water content.

1.4.1.4 Fluoroform Gas Handling

Fluoroform is a gas at temperatures higher than -82.1 °C and pressures greater than 1 atm. Two methods are used for transferring CF_3H into a reaction system (**Figure 1-6**). In Method A, a mixture of solvent and reactants is charged into a sealable (e.g., with a septum), heavy-walled, round-bottomed flask under inert gas atmosphere. The flask is cooled to 0 °C for 10 mins, and then the head of a long needle attached to a balloon filled with CF_3H gas was inserted and placed under the solvent level. Another short needle was inserted into the septum in order to release gas after the inside pressure of flask was balanced. Constant small bubbles indicated the injection of CF_3H. To prevent the access of air into the flask, the short needle must be removed before the long needle to the balloon of CF_3H when the injection of starting material(s) is complete. In Method B, a flask with solvent and reactants is frozen by immersion of the flask in liquid N_2, and then the contents of the flask are degassed three times and finally filled with CF_3H on the last cycle. The amount of CF_3H charged in flask is recorded after a quick measurement. Method A is normally used in a reaction in which CF_3H is added at the end of preparing the reaction mixture. Conversely, Method B is used for reactions in which base is added during the last step.

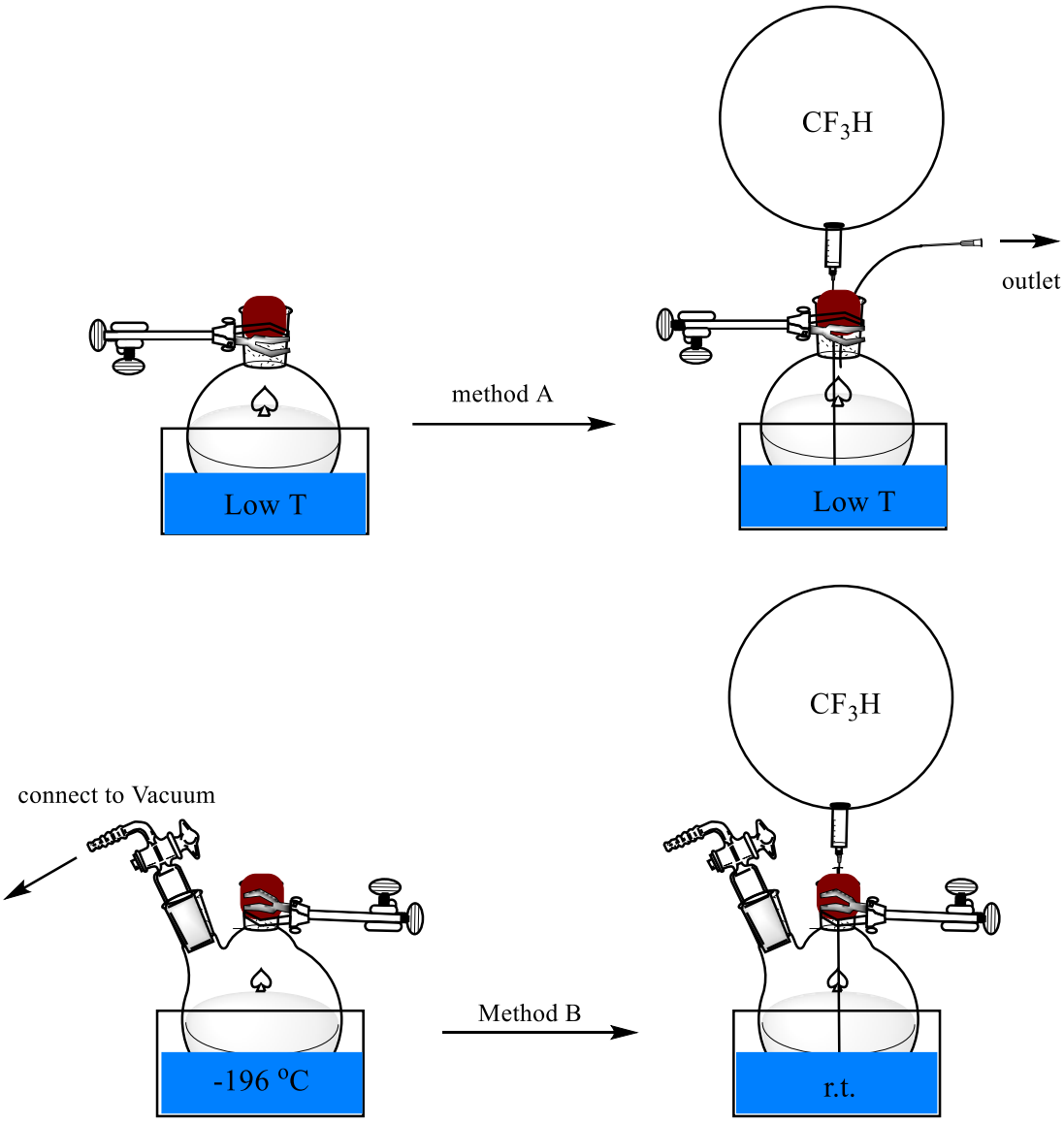


Figure 1-6. *Fluoroform gas handling.*

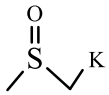
1.4.1.5 Nuclear Magnetic Resonance Spectroscopy

Hydrogen-1, fluorine-19, boron-11, carbon-13, and silicon-29 NMR spectra were recorded at ambient temperature with either a JOEL ECX 300 NMR instrument or a Bruker Avance 300 NMR instrument. The frequency and solvent used are described separately for each substance. NMR spectra were measured using solutions of 1-2 mmol/L concentrations in an appropriate deuterated solvent. All chemical shifts are given in units of the δ-scale in ppm. Chemical shifts for ^{1}H NMR spectra are given with respect to the proton signal of the solvent used (acetonitrile 1.94 ppm, chloroform 7.25 ppm, dimethyl sulfoxide 2.50 ppm, methanol 3.35 ppm, toluene 7.00 ppm, and water 4.75 ppm); for ^{13}C NMR spectra respective to the deuterated solvent used (acetonitrile 118.69 ppm, chloroform 77.0 ppm, dimethyl sulfoxide 37.7 ppm, and methanol 49.3 ppm). ^{19}F NMR chemical shifts were referenced to either $CFCl_3$ (0.00 ppm) or trifluorotoluene (-63.72 ppm). Dry NMR solvents are prepared using an appropriate drying agent followed by storage over molecular sieves (3 Å). The dry solvents were degassed and stored in glass bulbs fitted with glass-PTFE valves. Air-sensitive NMR samples are prepared in 5-mm o.d. J. Young NMR tubes, whereby the sample and dry solvent can be vacuum transferred into the NMR tube. Negative chemical shifts indicate upfield shifts, while positive chemical shifts indicate downfield shifts. The multiplicities of the signals are given by the following abbreviations: s (singlet), d (doublet), dd (doublet of doublets), td (triplet of doublets), q (quartet), quin (quintet), m (multiplet), and br (broad), and coupling constants are given in hertz (Hz).

1.4.1.6 Melting Points

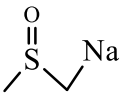
Melting points are measured in glass capillary tubes with a MEL-TEMP melting point apparatus and are uncorrected.

1.4.2 Synthesis of Dimsyl-K



KH/oil solution (25-30 wt%, 0.12 g) is transferred into a 10-mL flask via a pipet in the glove box filled with argon gas. hexane was transferred into the flask to remove the oil (5 mL/time, 3 times), and the resulting powder is dried under a flow of argon gas. The flask is weighed to record the amount of KH collected. The flask was cooled to 0 to -5 °C for 10 minutes. The flask is removed from cooling bath in order to return to room temperature after anhydrous DMSO (0.5 mL/mmol of KH) is slowly injected into the flask. The resulting reaction mixture is allowed to stir at room temperature until all of the solid KH dissolves and no more bubbles of hydrogen gas are being generated.

1.4.3 Synthesis of Dimsyl-Na



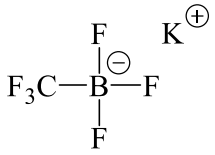
NaH/oil power (60 wt%, 0.18 g) is transferred into a 10-mL flask in the glove box filled with argon gas. Hexane was transferred into the flask to remove the oil (5 mL/time, 3 times), and the resulting powder is dried under a flow of argon gas. The flask is weighed

to record the amount of NaH collected. Anhydrous DMSO is slowly injected into the flask. The reaction mixture is heated to 75 °C with stirring. The resulting reaction mixture is returned to room temperature whereby the NaH remains completed dissolved and no more bubbles of hydrogen gas are being generated.

1.4.4 Synthesis of Trifluoromethyl(trimethyl)silane (1)

To a 20-mL three-necked, round-bottomed flask with a magnetic stirrer is added 10 mL of THF. The flask is cooled to 0 to -5 °C for 10 minutes. Fluoroform (0.44 g, 6.3 mmol) is bubbled into this THF solution for 5 minutes. The mass of the flask is then quickly measured and recorded. The flask is placed into an acetone/dry ice bath and cooled to -80 °C for 20 minutes. Anhydrous chlorotrimethylsilane (0.40 mL, 3.2 mmol) is then added to solution, which is stirred for 10 minutes. A fleshly prepared solution of dimsyl-K (3.2 mmol) is then added dropwise to the reaction mixture. Then more CF_3H is slowly bubbled into the reaction mixture through a balloon for another 5 minutes. After the addition of CF_3H is over, the resulting reaction mixture is stirred vigorously at -80 °C for 5 hours. The resulting reaction mixture is then slowly warmed to room temperature and stirred for an additional 2 hours. A sample of the reaction mixture is taken for investigation by NMR spectroscopy. ^{1}H NMR (400 MHz): δ 0.27 (s); ^{13}C NMR (100.5 MHz): δ -5.18 (s, CH_3), 132.23 (q, $^{1}J_{C\text{-}F}$ = 322 Hz, CF_3). ^{19}F NMR (376.3 MHz): δ -67.3 (s); ^{29}Si NMR (79.5 MHz): δ 4.1 (q, $2J_{Si\text{-}F}$ = 37.9 Hz, 1 Si).

1.4.5 Synthesis of Potassium (Trifluoromethyl)trifluoroborate (3)



Dry THF (10 ml) is added into a 25-mL flask with a magnetic stir bar under argon atmosphere. The flask is then cooled to 0 to -5 °C for 10 minutes. Fluoroform (0.56 g, 8.0 mmol) is bubbled into this THF solution for 5 minutes. The reaction mixture is stirred at -80 °C for ten minutes. Then trimethoxyborane (1.2 mL, 9.2 mmol) is added to the reaction mixture. The resulting reaction mixture is stirred for an additional 5 minutes. Then a solution of dimsyl-K (4.6 mmol) is added dropwise to the reaction mixture, and the resulting yellowish reaction mixture is stirred at -80 °C for 4 hours. The reaction mixture is then warmed slowly to room temperature. The solvent is removed via rotary evaporation. The crude product obtained is then transferred to a PTFE bottle. This bottle is cooled in an ice bath and then aqueous hydrogen fluoride (48 wt%, 2.76 mL) is added. The resulting reaction mixture is stirred at room temperature for 12 hours. Thereafter, a solution of potassium hydroxide (10 wt%) is slowly added to the reaction mixture until it is slightly acidic. Potassium bicarbonate is then added portion-wise into the reaction mixture until the pH of the reaction mixture is greater than 7 and the evolution of CO_2 has ceased. Then water is removed under vacuum, and the remaining solid is ground to give a white powder. The powder is transferred into the boiling acetonitrile and filtered. Acetonitrile is removed via rotary evaporation, and the pure product is collected as a white powder. ^{19}F NMR (376.3

MHz, D_2O): δ -76.7 (q, J = 33.6 Hz, CF_3), -155.0 (q, J = 40.7 Hz, 3 F); ^{11}B NMR (128.3 MHz, D_2O): δ 0.8 (q, $^1J_{B\text{-}F}$ = 40.7 Hz, 1 B).

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CHAPTER TWO

PENTAFLUOROSULFANYLATION

2.1 Introduction

2.1.1 Physical Properties of the Pentafluorosulfanyl Group

In 1962, Sheppard first reported the properties of the pentafluorosulfanyl group (SF_5).[1] After that, compounds containing the SF_5 group have been attracting great interest because of their potential applications in medicinal, agrochemical, and materials chemistry.[2] The SF_5 group has been considered as a potentially superior replacement for the trifluoromethyl group due to the peculiarity of fluorine, and this group is called a "super-trifluoromethyl group" (**Table 2-1**). However, the development of SF_5 chemistry in the past 60 years has been slow because of the lack of commercially available SF_5 starting materials. Recently, the synthesis of organic molecules containing this functional group has gained increasing attention. Several recent publications further proved the possibility that the replacement of a CF_3 group with a SF_5 group in organic molecules can greatly change their potency and/or selectivity in bio-system.[3-5]

Table 2-1. *Properties of the pentafluorosulfanyl group compared with those of the trifluoromethyl group*[3-4]

	SF_5	CF_3
Volume* ($Å^3$)	-11.1	-34.9
Lipophilicity (π_x)	1.5	1.07
Electronegative (σ_I)	+0.55	+0.39

*Compare with *tert*-butyl, volume = V(CF_3/SF_5) – V(*t*-Bu)

The first preparation of the pentafluorosulfanyl substituent was reported in 1933 after the discovery of the dimer of SF_5, disulfur decafluoride (S_2F_{10}), as a by-product from the synthesis of sulfur hexafluoride (SF_6) by exposure of S_8 to F_2.[6-7] The pentafluorosulfanyl group has a hypervalent hexacoordinated sulfur atom with an octahedral geometry, and thus, SF_5-carbon bonded molecules are considered as organic derivatives of SF_6. The fluorine atoms of a SF_5 group display a characteristic AB_4 spin pattern in the ^{19}F NMR spectrum with one axial and four equatorial fluorine atoms as shown in **Figure 2-1**.[8] The distinct structure of the SF_5 group can be easily observed by a ^{19}F NMR investigation, where the $^2J(F_{ax}\text{-}F_{eq})$ coupling constant usually ranges between 145 to 155 Hz. Meanwhile, a pentafluorosulfanyl group is much larger than a trifluoromethyl group, but smaller than a *tert*-butyl (*t*-butyl) group. When compared with *tert*-butyl and trifluoromethyl groups, the order of "volume" is as follows: $\Delta V\,(CF_3) = -34.9$ Å^3 < $\Delta V\,(SF_5) = -11.1$ Å^3 < $\Delta V\,(t\text{-Bu}) = 0$ Å^3 ($\Delta V = V_{substituent} - V_{t\text{-Bu}}$).[9] However, with the octahedral bond angles around the sulfur(VI) atom in a SF_5 group, the group probably requires a larger cone angle or steric sweep than does a *t*-butyl group. Furthermore, the preparation of organic molecules containing a pentafluorosulfanyl group gives researchers more flexibility by which to modify the properties of target compounds, examples are shown in section 2.1.4.

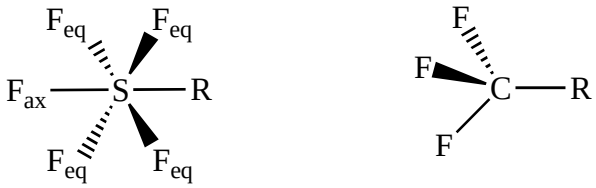


Figure 2-1. *Structures of SF_5- and CF_3-containing molecules.*[8]

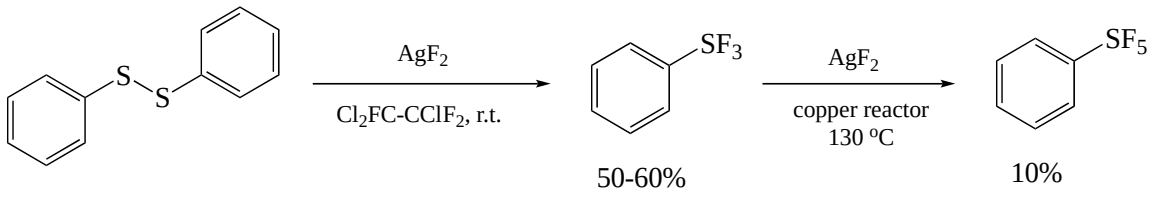
Moreover, the pentafluorosulfanyl group has a high lipophilicity due the group containing five fluorine atoms. The measurement of Hansch hydrophobicity constants from several substituted benzenes proved the SF_5 substituent [$\pi(SF_5)$ = 1.23] to be more lipophilic than a CF_3 group [$\pi(CF_3)$ = 0.88] or a trifluoromethoxy group [$\pi(OCF_3)$ = 1.04].[10] However, the SF_5 group is less lipophilic than the trifluoromethylthio group [$\pi(SCF_3)$ = 1.44] or the *t*-butyl group [π(*t*-Bu) = 1.98]. On the other hand, the pentafluorosulfanyl group has the strongest electron withdrawing effect. A comparison of the dissociation constants of *meta*- and *para*-substituted benzoic acids with Hammett parameters σ_m and σ_p is shown as **Table 2-2**.[1,11-13]

Table 2-2. *Dissociation constants and Hammett and Hansch parameters*[1,11-13]

X	pK_a (*meta*)	pK_a (*para*)	σ_m	σ_p	Hansch Lipophilicity
NO_2	4.66	4.53	0.73	0.77	-0.28
SF_5	4.82	4.70	0.61	0.69	1.23
SCF_3	5.13	4.98	0.41	0.51	1.44
OCF_3	5.15	5.19	0.39	0.36	1.04
CF_3	5.11	4.95	0.43	0.53	0.88

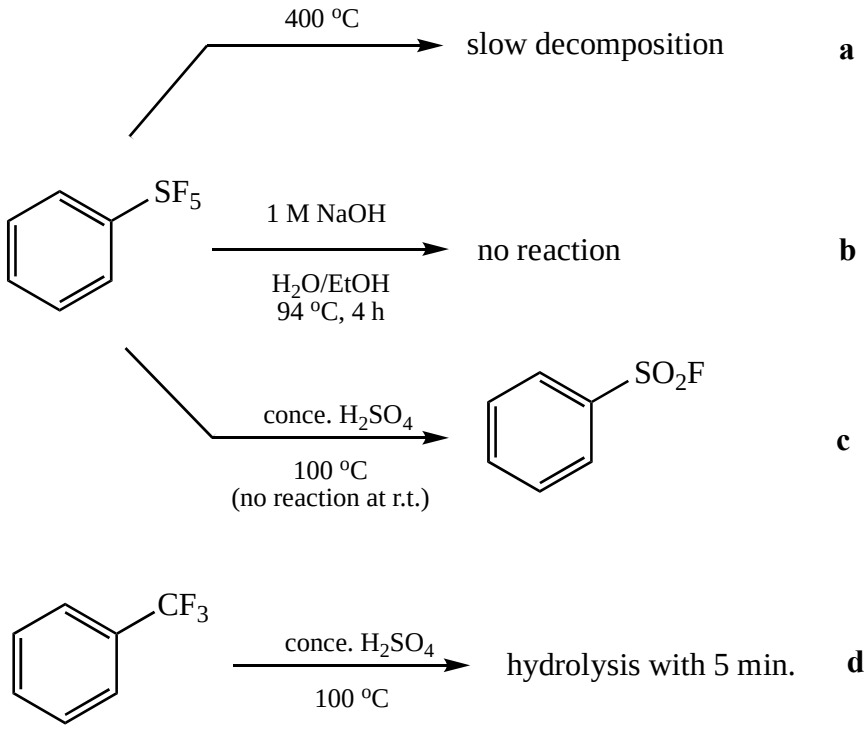
2.1.2 Chemical Stability of the Pentafluorosulfanyl Group

In 1960, Sheppard *et al*. completed a set of experiments to study the chemical stability of pentafluorosulfanylbenzene (Ph-SF_5) by stepwise oxidative fluorination of the corresponding phenyl disulfide (**Scheme 2-1**).[14] The first preparation of Ph-SF_5 started



Scheme 2-1. *First preparation of pentafluorosulfanylbenzene.*[14]

with the treatment of phenyl disulfide with silver difluoride (AgF_2) in 1,1,1-trichloro-trifluoroethane. The generated phenylsulfur trifluoride was collected and heated up to 130 °C in a copper reactor in the presence of AgF_2 to give the isolated Ph-SF_5 in about 10% yield after distillation. Ph-SF_5 showed good thermal stability with only minor degradation occurring after being heated at 400 °C for several hours (**Scheme 2-2**, Path a).[15] The release of fluoride ion was not detected after the treatment of Ph-SF_5 with 1M NaOH in aqueous



Scheme 2-2. *Chemical and thermal stability of the SF_5 group.*[15-16]

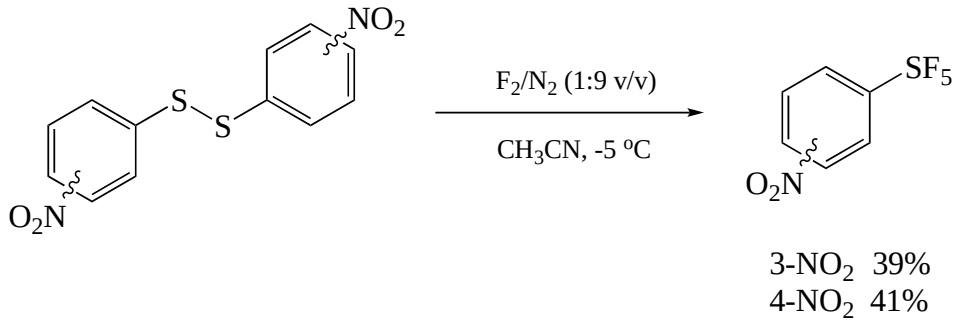
ethanol after 4 hours of refluxing at 94 °C (**Scheme 2-2**, Path b). Ph-SF_5 was even proved to be inert in concentrated sulfuric acid (H_2SO_4) at room temperature. The hydrolysis of Ph-SF_5 in concentrated H_2SO_4 started at around 100 °C. On the other hand, the corresponding trifluorotoluene (Ph-CF_3) was completely decomposed within 5 minutes under the same reaction conditions (**Scheme 2-2**, Paths c and d).[16]

2.1.3 Synthesis of Pentafluorosulfanylated Compounds

2.1.3.1 Synthesis of Pentafluorosulfanylated Aromatic Compounds

As previously stated, Sheppard reported the first synthesis of phenylsulfur pentafluoride by the fluorination of diphenyl disulfide with silver difluoride (**Scheme 2-1**).[14] This approach was applied to prepare some other pentafluorosulfanylated aromatic compounds.[15] However, the development of SF_5-aromatic chemistry was almost stopped because of poor reproducibility and the requirement of excess amounts of expensive AgF_2 in Sheppard's method.

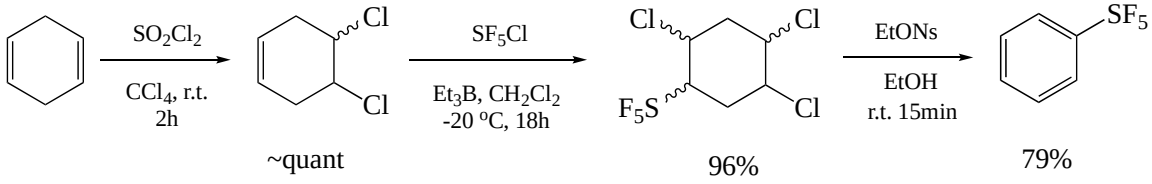
In 2000, Bowen and Philp achieved a significant advance in SF_5-aromatic chemistry by the direct fluorination of appropriate precursors with elemental fluorine (F_2/N_2 = 1/9) (**Scheme 2-3**).[16-17] For example, the diluted F_2 was reacted with bis(*p*- or *m*-nitrophenyl) disulfide at low temperature to give the corresponding SF_5-arenes in reasonable yield (39-41%). Though F_2 is corrosive, this method was commercially used to produce SF_5-substitued nitrobenzenes due to the reasonable yield and convenient process.



Scheme 2-3. *Synthesis of m- or p-nitrophenylsulfur pentafluoride using elemental fluorine.*[16-17]

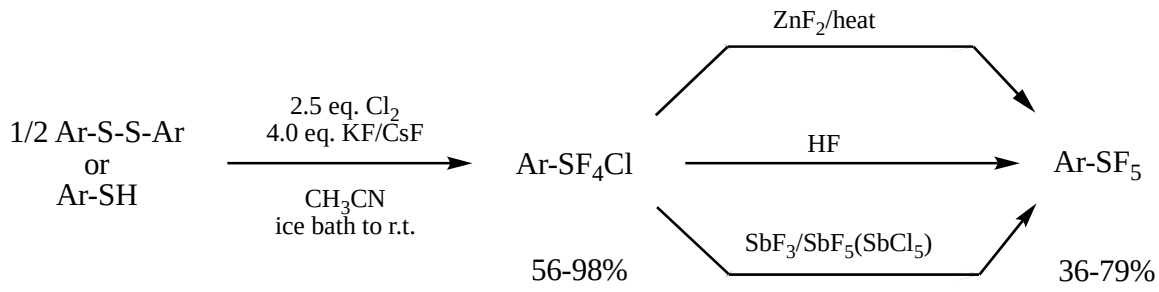
Later, Thrasher *et al*. applied Sheppard's method to synthesize phenylsulfur pentafluoride compounds with substituents other than nitro.[18-19] Thrasher also mentioned the necessity of the presence of copper for Sheppard's reaction to succeed.[20]

In 2004, Dolbier *et al*. used triethylborane (Et_3B) as a radical initiator for the addition reaction of pentafluorosulfanyl chloride (SF_5Cl) to prepare SF_5-benzene (**Scheme 2-4**).[21] This method can be easily carried out in common glassware at low temperature with high yield (>70%). However, the high price of SF_5Cl limited the application of this three-step method.



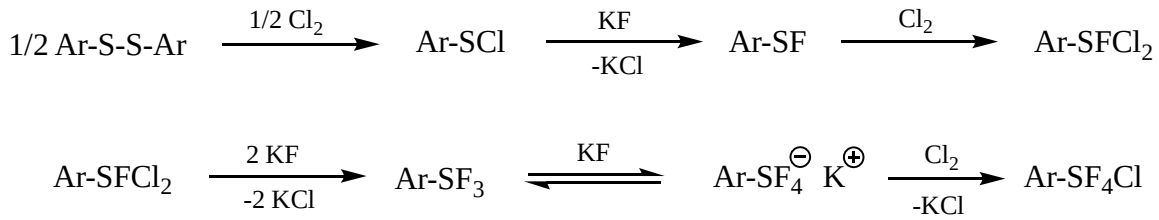
Scheme 2-4. *Synthesis of SF_5-benzene from SF_5Cl gas.*[21]

In 2008, Umemoto *et al*. made a key contribution to SF_5-aromatic chemistry. He developed the first practical and economical route to prepare aryl sulfurpentafluorides ($ArSF_5$).[22-23] The two-step method did not use elemental fluorine. A solution of



Scheme 2-5. *Umemoto's preparation of SF_5-benzenes.*[22-23]

commercially available phenyl disulfide or thiol was treated with chlorine (Cl_2) in the presence of dry potassium fluoride (KF) at room temperature to generate arylsulfur chlorotetrafluoride intermediates ($ArSF_4Cl$). The purified $ArSF_4Cl$ compounds were then converted into the corresponding SF_5-aryl products by displacement of the chloride with a fluoride source, such as zinc difluoride (ZnF_2), HF, or SbF_3 and SbF_5 (**Scheme 2-5**). Since this procedure utilized commercially available reagents, Umemoto's method has been scaled up in industry to exhibit a great substrate scope for preparing SF_5-benzenes and their derivatives. In the reaction mechanism proposed by Umemoto as shown in **Scheme 2-6**, the introduction of chlorine in first four steps to generate $Ar\text{-}SF_3$ are fast reactions. The existence of this intermediate was confirmed by ^{19}F NMR spectral investigations of the reaction mixture. The sequence of the last two steps to give the final product $Ar\text{-}SF_4Cl$ is slow. The rate-determining step may be the formation of $Ar\text{-}SF_4^-K^+$ which is generated from $Ar\text{-}SF_3$ via an equilibrium reaction.

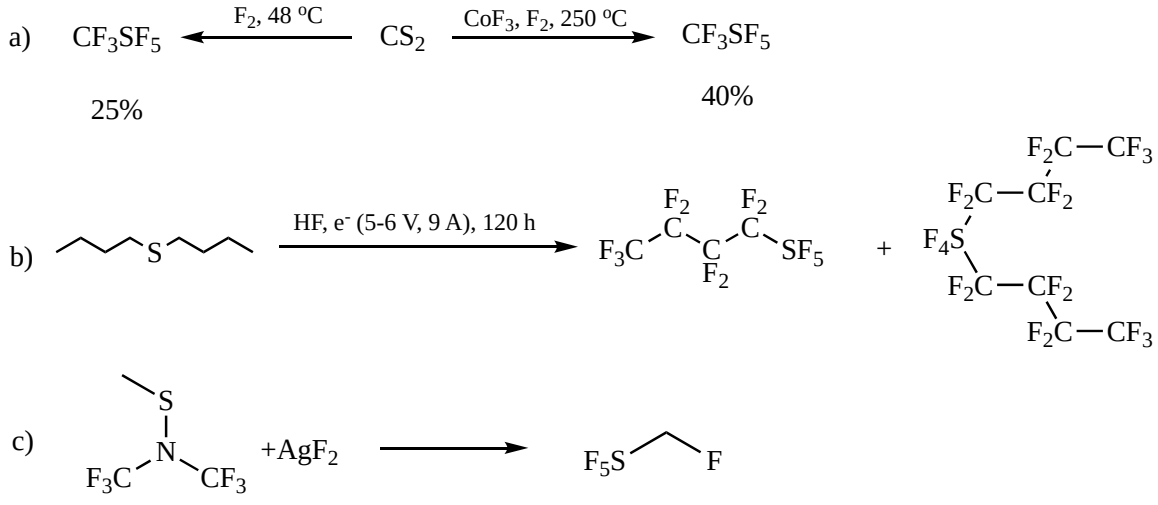


Scheme 2-6. *Proposed mechanism for the formation of $ArSF_4Cl$.*[22]

Very recently, Shibata and co-workers described the synthesis of unsymmetrical diaryliodonium reagents having 2-SF_5-pyridine using Umemoto's method as the key reaction. These reagents were proved to be the efficient electrophilic reagents for the transformation of SF_5-pyridyl group to carbon and hetero-centered nucleophiles in good to excellent yields.[24]

2.1.3.2 Synthesis of Pentafluorosulfanylated Aliphatic Compounds

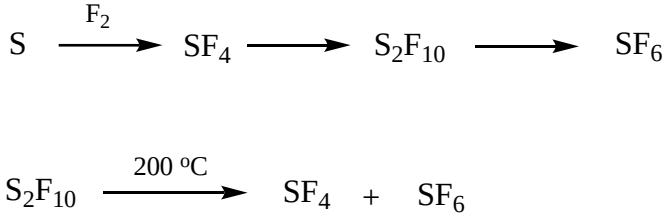
The first direct synthesis of SF_5-alkyl compounds started in the 1950s with the preparation of the smallest pentafluorosulfanylated compound (SF_5CF_3) from the fluorination of CS_2 with elemental F_2.[25] The yield of SF_5CF_3 was improved to 40% when reaction was carried out in the presence of CoF_3 (**Scheme 2-7**, Path a).[26] After this report, the electrochemical fluorination in HF was also applied on the same process (**Scheme 2-7**, Path b).[27-31] Silver difluoride was also used in the fluorination of *N*,*N*-bis(trifluoromethyl)-sulfenamide to prepare the fluoromethyl analogue in good yield (86%) (**Scheme 2-7**,



Scheme 2-7. *Direct fluorination of sulfur-containing compounds.*[26-32]

Path c).[32] However, direct fluorination methods requiring toxic or expensive fluorination reagents were not widely applied.

Most pentafluorosulfanylated alkyl derivatives are synthesized by the radical addition of SF_5X (X = Cl, Br, SF_5) to the corresponding unsaturated compounds. As mentioned above, Ruff discovered the formation of disulfur decafluoride (S_2F_{10}) as a minor side product during the preparation of sulfur hexafluoride (SF_6) by fluorination of S_8 with F_2.[33-34] The compound S_2F_{10} does not readily react with water or metals at room temperature, but it is completely decomposed to a mixture of sulfur tetrafluoride (SF_4) and SF_6 at 200 °C (**Scheme 2-8**).[35] Disulfur decafluoride has also been prepared directly by the photochemical transformation of both pentafluorosulfanyl chloride (SF_5Cl) and pentafluorosulfanyl bromide (SF_5Br).[36-38] Disulfur decafluoride is four times as toxic as phosgene, and it was considered as a potential chemical pulmonary agent during World War II.[39]



Scheme 2-8. *Formation and decomposition of S_2F_{10}.*[35]

Compare to disulfur decafluoride, pentafluorosulfanyl chloride is easier to synthesize, and this compound also has a lower toxicity. Therefore, it has been a very important reagent for transferring the pentafluorosulfanyl group into organic molecules. The initial methods for the synthesis of SF_5Cl in 1959 was based on the treatment of S_2F_{10} with chlorine gas (**Scheme 2-9**).[40] Later, several methods were reported for the improved

preparation of this reagent. Nyman claimed a more convenient method consisting of the reaction of ClF_3, Cl_2 and SF_4 to prevent the use of S_2F_{10} in 1962.[41] This reaction was successfully scaled up to produce 660 g of SF_5Cl from 520 g of SF_4 (85% yield). Further optimization of this approach was found by decreasing the reaction temperature in the presence of MF (M = Cs or K). The role of MF is to form a complex with SF_4, namely $M^+SF_5^-$, which can be more easily oxidized by ClF.[42-43] Winter *et al*. recently reported a practical and economical route for preparing SF_5Cl in excellent yield (95%).[44] In this

1959 (Cotton)

$$S_2F_{10} + Cl_2 \xrightarrow[\text{r.t.}]{} SF_5Cl$$

1962 (Nyman)

$$ClF_3 \xrightarrow[350\ ^oC]{Cl_2} ClF \xrightarrow[375\ ^oC]{SF_4} SF_5Cl \quad 85\%$$

1964 (Muetterties)

$$SF_4 \xrightarrow[110\ ^oC \text{ to } 175\ ^oC]{CsF,\ Cl_2} SF_5Cl \quad 75\%$$

1998 (Seppelt)

$$SF_4 \xrightarrow[\substack{75\ ^oC,\ 3\ d \\ \text{then } 150\ ^oC,\ 6\ d}]{KF,\ Cl_2} SF_5Cl \quad 90\%$$

2009 (Winter)

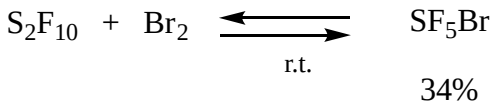
$$KF + S_8 + Cl_2 \xrightarrow[\text{r.t., 2-3 weeks}]{Br_2} SF_5Cl \quad 95\%$$

Scheme 2-9. *Synthesis of SF_5Cl.*[40-44]

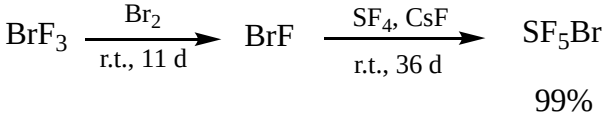
method, elemental sulfur, dry KF, and Cl_2 are reacted in the presence of bromine at room temperature for two to three weeks. No SF_5Cl is formed in the absence of Br_2. After such developments in the synthesis of SF_5Cl, it has become the only commercially available SF_5-containing reagent for the direct introduction of the SF_5 group.

When compared to SF_5Cl, pentafluorosulfanyl bromide is both less stable and more challenging to prepare and purify. The first preparation of SF_5Br in 1962 (34% yield) was based on the addition of Br_2 to S_2F_{10} as reported for SF_5Cl (**Scheme 2-10**).[45] The drawback of this method is that the S_2F_{10} is not completely consumed even when using a large excess of Br_2 at 150 °C. In part, this might be due to S_2F_{10} being regenerated from the decomposition of SF_5Br at too high of a reaction temperature. Winter and Gard reported an improved method to form SF_5Br in 99% yield with the use of BrF as a starting material.[46] Bromine monofluoride was generated by the reaction of Br_2 and BrF_3 in a metal reactor.

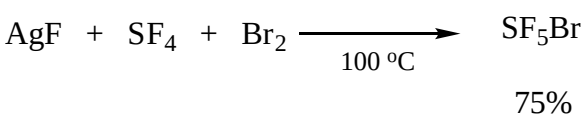
1965 (Cohen/MacDiarmid)



1998 (Winter/Gard)



2009 (Winter)



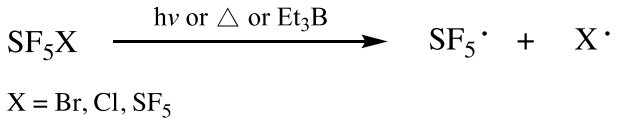
Scheme 2-10. *Synthesis of SF_5Br.*[44-46]

Winter *et al*. recently disclosed a new process for generating SF_5Br in 75% yield by heating silver fluoride (AgF), SF_4, and Br_2 at 100 °C.[44]

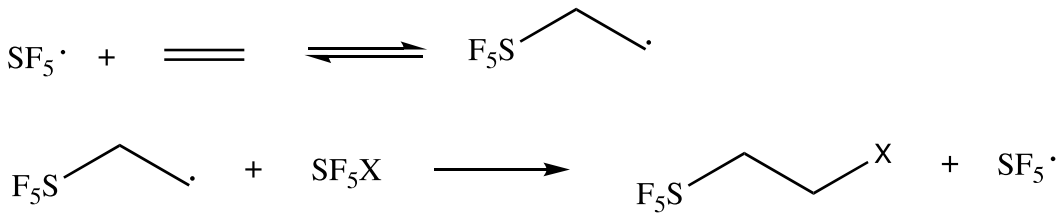
The compound SF_5Br is the most reactive of the three pentafluorosulfanylating reagents described above. However, it has the lowest thermal stability, and it is more difficult to prepare. While the decomposition of SF_5Br starts at 150 °C, SF_5Cl is stable up to 400 °C.[47-48] Therefore, the more reactive SF_5Br is used directly in reactions with light or mild heating to generate the pentafluorosulfanyl radical. On the other hand, the less reactive SF_5Cl is used in the presence of a peroxide catalyst to start the SF_5-radical addition.[49]

The mechanism for the general free radical addition of SF_5X (X = Br, Cl, SF_5) to alkenes is shown in **Scheme 2-11**.[50] The SF_5• radical is generated under photochemical, thermal conditions, or chemical means in the initiation step, which is followed by the

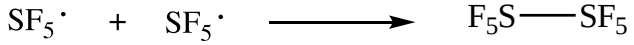
Initiation



Chain propagation



Termination



Scheme 2-11. *General mechanism for the free radical addition of SF_5X (X = Br, Cl, SF_5).*[50]

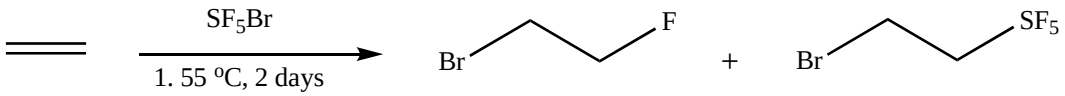
addition reaction of both the SF_5• and X• radicals to molecules containing either a double or triple bond. A termination step is found in the formation of S_2F_{10} where two SF_5· radicals combine together.

In 1961, Case *et al*. first applied thermal and photochemical conditions to achieve the radical addition of SF_5Cl to alkenes in good yields (**Scheme 2-12**).[51] However, the extremely high reaction pressure used in this method gave polymerization products from either 2-methylpropene or styrene.

47-78 %

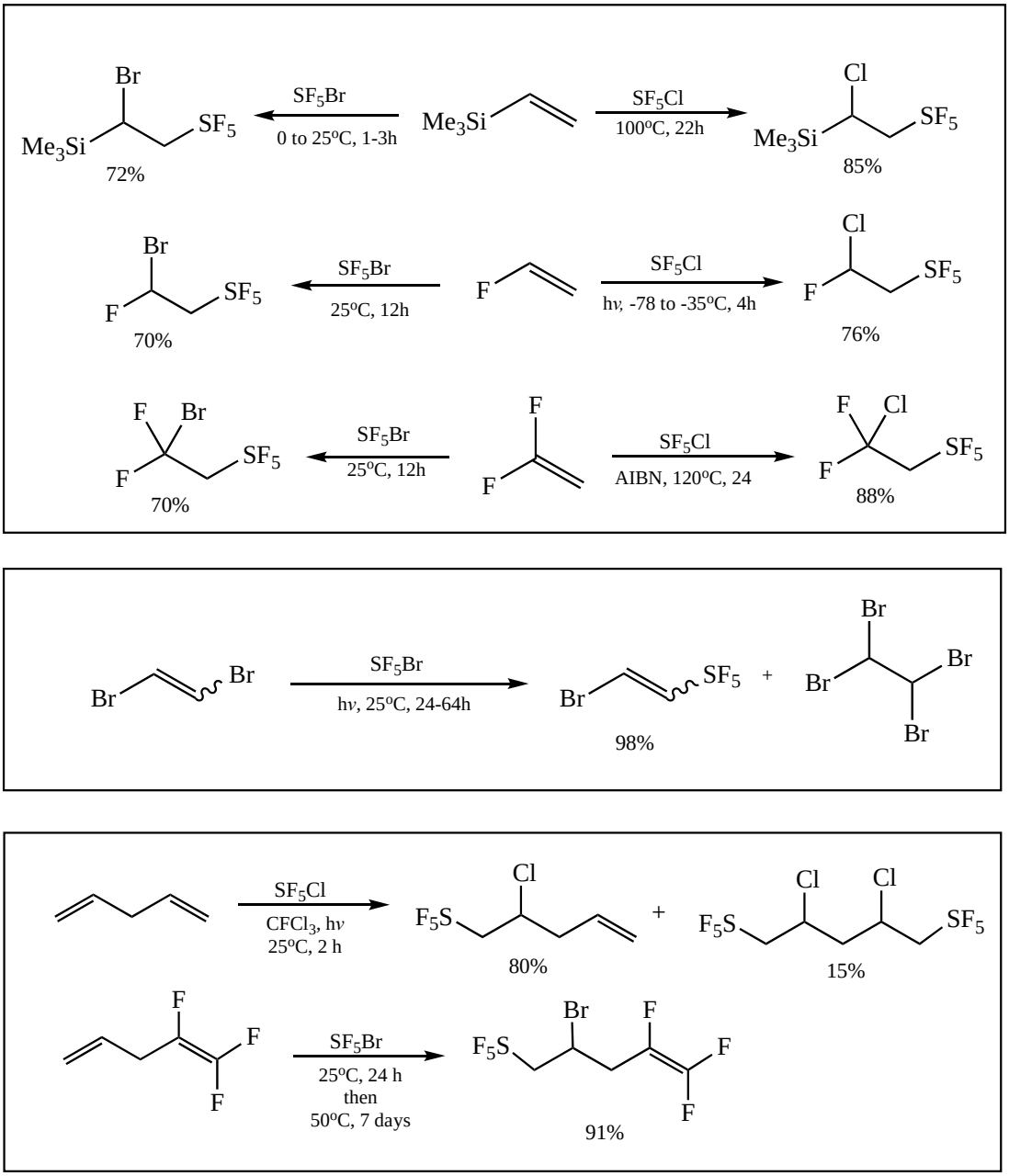
Scheme 2-12. *First radical addition of SF_5Cl to alkenes.*[51]

Some special characteristics exist between the addition reactions using SF_5Br and SF_5Cl. The more reactive SF_5Br is harder to control in the thermal addition to ethylene. The yield of the target SF_5-product was only 9% from Gard's report in 1987 (**Scheme 2-13**).[52] In the following years, SF_5Br and SF_5Cl were used to introduce the pentafluorosulfanyl group into olefins under thermal conditions. From the examples shown in part a of **Scheme 2-14**,[53-57] the reactions using SF_5Cl as the source of the SF_5 group gave slightly better yields than with examples using SF_5Br. But with the use of SF_5Br, one can often significantly decrease the reaction temperature and shorten the reaction time. The



Scheme 2-13. *Attempted addition of SF_5Br to ethylene.*[52]

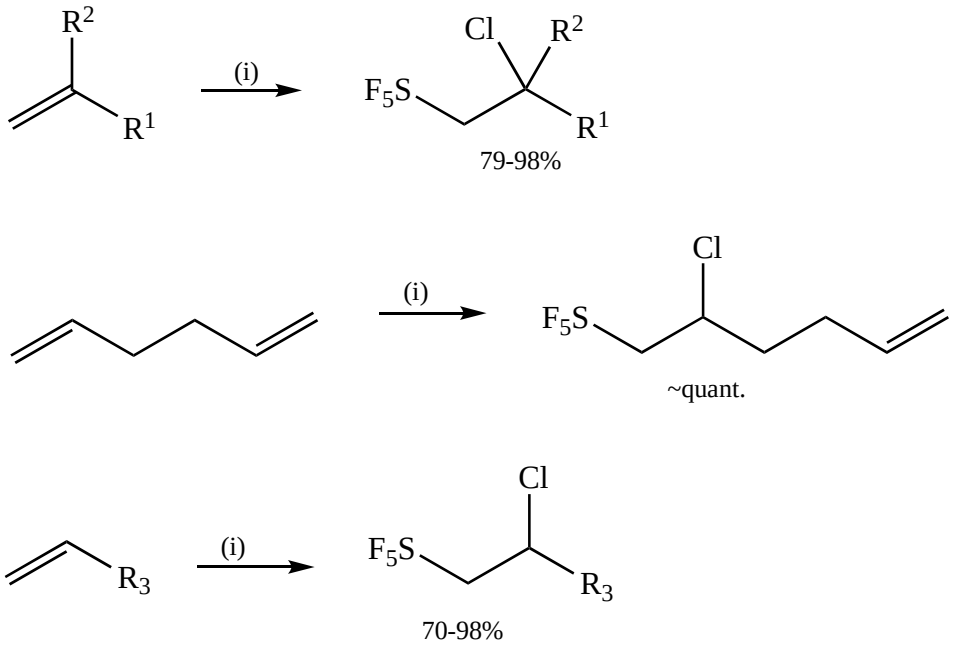
addition reaction of SF_5Br to 1,2-dibromoethylene gave a possible radical exchange process by yielding 1,1,2,2-tetrabromoethane as a by-product in the reaction mixture (**Scheme 2-14**, part b). The SF_5• radical is more favored to add to more electron-rich double bonds in compounds that have more than one double bond. When SF_5Cl was reacted with



Scheme 2-14. *Addition of SF_5X (Br, Cl) to double bonds.*[53-57]

dienes containing two terminal double bonds, the main products resulted from the mono addition of the SF_5 group (**Scheme 2-14**, part c).[57] When SF_5Br was reacted with a diene containing one double bond substituted with three fluorine atoms, the main product had the SF_5 group attached to the non-fluorinated double bond.[58]

In 2002, a breakthrough in the SF_5-addition reactions was reported by Dolbier and coworkers.[59] Dolbier discovered that Et_3B was an excellent radical initiator for the addition of SF_5Cl to alkenes and alkynes (**Scheme 2-15**). This novel method can be easily carried out in common glassware at low temperature with high yield. Dolbier's method was quickly applied by other researchers to synthesize a variety of functionalized pentafluorosulfanylated derivatives.[60-62]

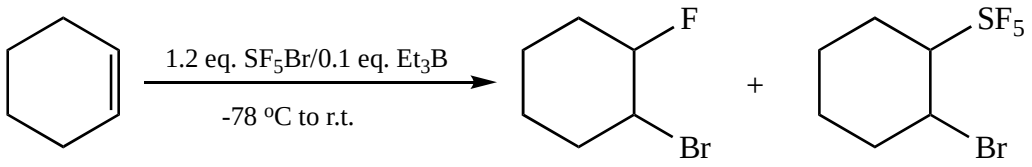


R^1 = *n*-C_6H_{13}, *n*-C_4H_9, *i*-C_4H_9, C_2H_5, *p*-tolyl
R^2 = H, C_2H_5
R^3 = OAc, $(CH_2)_nCOOEt$ (n=1 or 2), $(CH_2)_2COCH_3$, $(CH_2)_8OH$, $(CH_2)_8OAc$, $(CH_2)_8Br$

Condition (i): SF_5Cl, Et_3B (cat.), hexane, -30 °C

Scheme 2-15. *Et_3B catalyzed additions of SF_5Cl to unsaturated compounds.*[59]

However, the radical addition of SF_5Br in the presence of Et_3B was limited to the application of electron-deficient alkenes.[60] When the substrates were nucleophilic, undesired compounds resulting from the addition of BrF were observed as the main products (**Scheme 2-16**). Welch improved upon procedure by using a non-polar solvent, such as CCl_3F to limit the amount of the BrF addition product.[63]



solvent: $CClF_3$	40%	60%
polar solvent	90%	10%

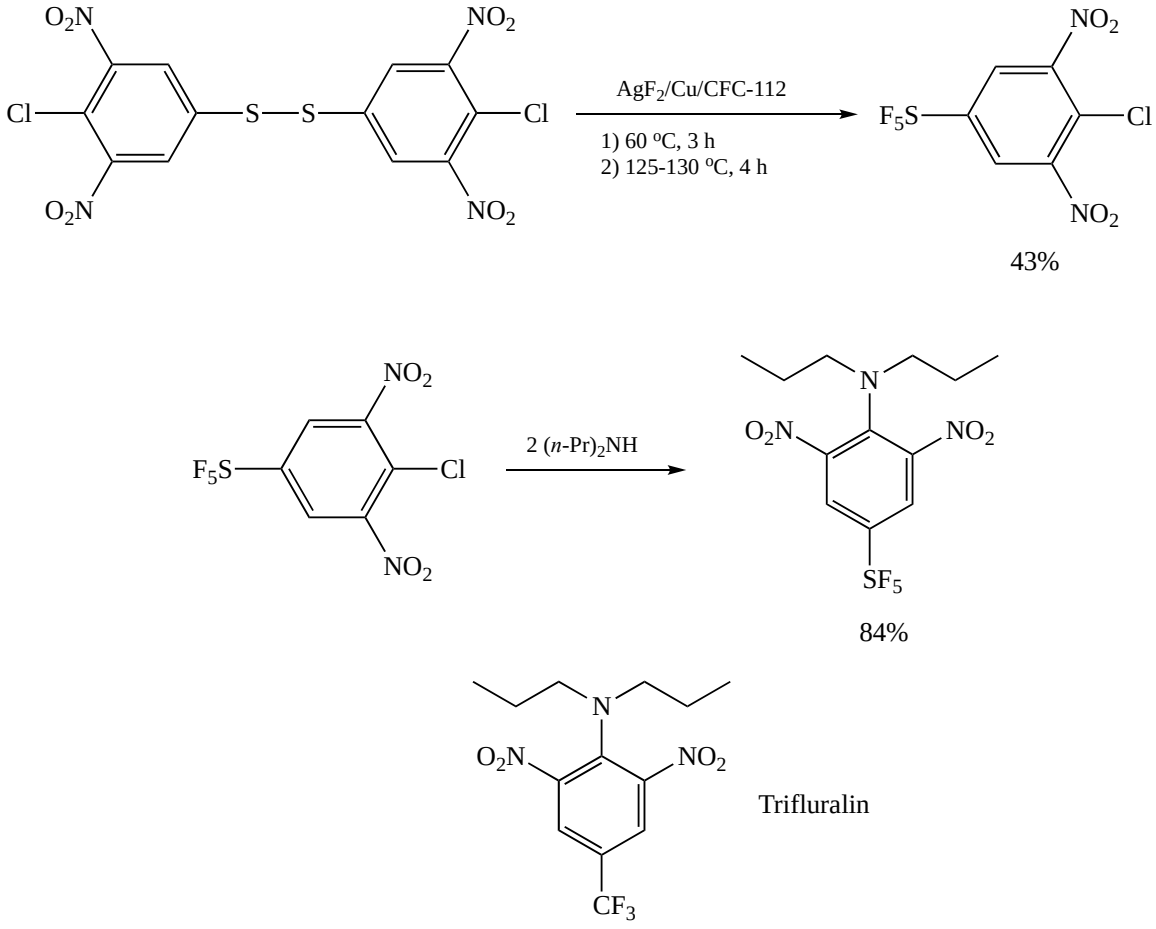
Scheme 2-16. *Et_3B catalyzed addition of SF_5Br to cyclohexene.*[60]

2.1.4 Applications of Pentafluorosulfanyl Chemistry

2.1.4.1 Agrochemical Applications

In 1963, a patent claimed the first application of pentafluorosulfanylarenes in the life sciences.[64] Since then many patents have disclosed the utility of pentafluorosulfanyl-containing compounds as pesticides, herbicides, fungicides, parasiticides, and insecticides.[65] One representative example is the pentafluorosulfanylated analogue of the herbicide trifluralin. Trifluralin is a widely-used herbicide for pre-emergence control of grass. In 2004, Thrasher *et al*. first synthesized this compound from bis(4-chloro-3,5-

dinitrophenyl)disulfides (**Scheme 2-17**).[19] A direct comparison of the herbicidal activity of the SF_5-analogue with that of the original trifluralin containing the CF_3-group was reported by Welch *et al*.[66] The SF_5-analogue of trifluralin exhibited almost two times the potency. In the pre-emergence screening, the SF_5-substituted trifluralin had approximately five-fold more activity against quackgrass and crabgrass than the parent trifluralin.



Scheme 2-17. *Trifluralin and its SF_5-analogue.*[19]

2.1.4.2 Medical Applications

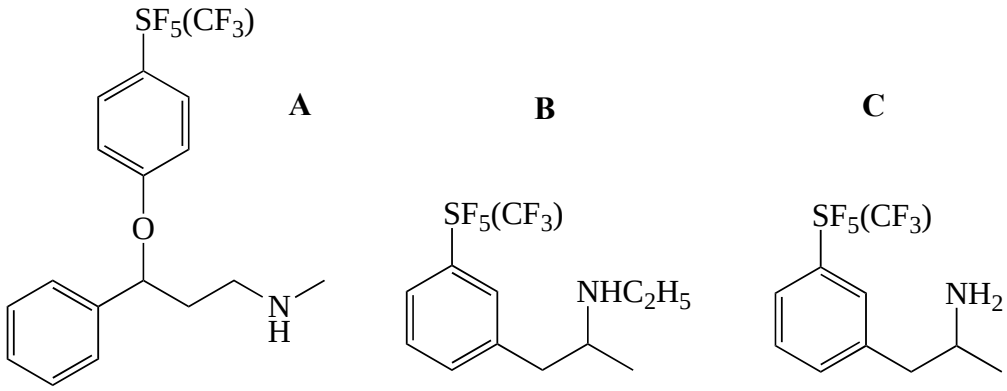


Figure 2-2. *SF_5- and CF_3-substituted analogs of fluoxetine, fenfluramine, and norfenfluramine.*[67]

Pentafluorosulfanyl-substituted analogs of fluoxetine (**Figure 2-2**, A), fenfluramine (**Figure 2-2**, B), and norfenfluramine (**Figure 2-2**, C) were prepared by Welch's group as well.[67] All of the parent compounds containing the trifluoromethyl group have been widely used as serotonin (5-hydroxytryptamine, 5-HT) inhibitors. Investigations of their bioactivity indicated that the SF_5-substituted compounds had improved on selectivity on inhibition toward 5-hydroxytryptamine receptors. The SF_5-modified norfenfluramine showed a significant improvement against 5-HT_{2b}, 5-HT_{2c}, and 5-H_{T6} receptors.

In 2009, Wipf *et al*. first reported a five-step sysnthetic route for preparing pentafluorosulfanyl analogs of mefloquine (**Figure 2-3**).[68] Mefloquine is a CF_3-containing quinoline, and it is the drug of choice for the treatment of malaria by the U.S. military. The SF_5-modified melfoquine A was found to have a better selectivity than the corresponding

mefloquine, and it demonstrated an equivalent or lower IC_{50} and IC_{90}. The SF_5-modified mefloquine B had an equivalent IC_{50} and IC_{90} when compared to the parent mefloquine.

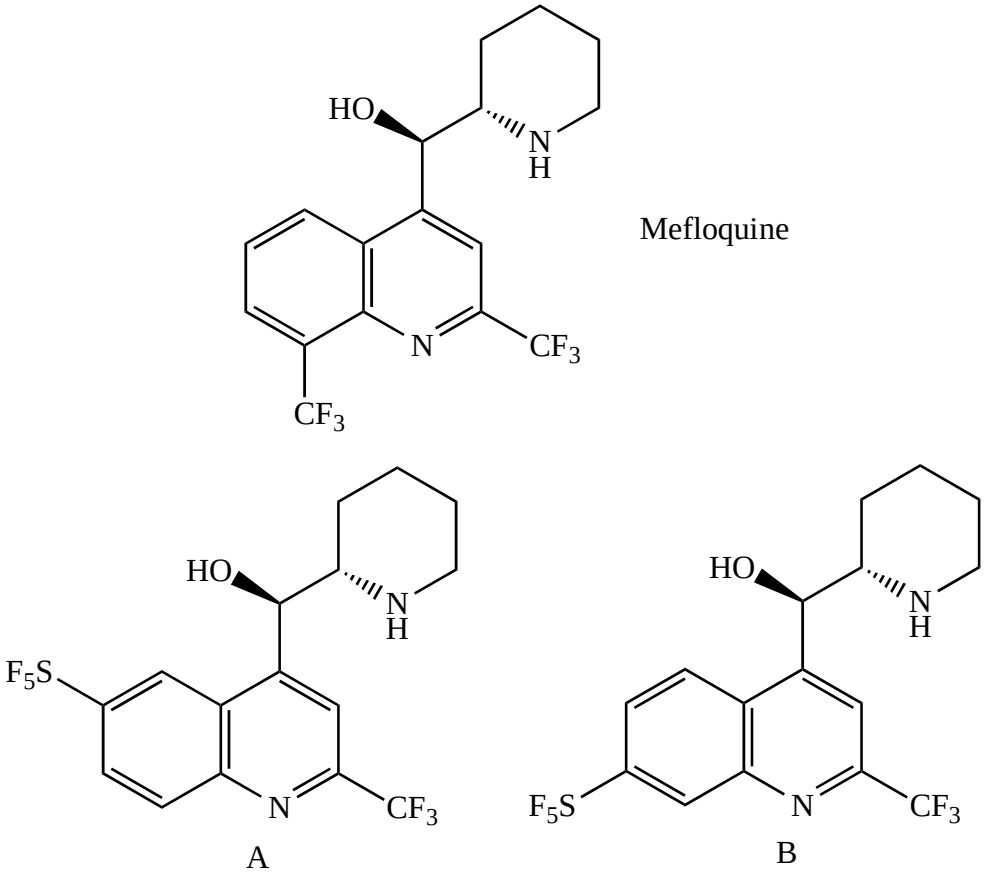


Figure 2-3. *SF_5-containing mefloquine.*[68]

Recently, Hendriks *et al*. reported the two-step preparation of pentafluorosulfanylated flufenamic acid analogues (**Figure 2-4**) from pentafluoro-sulfanylanilines.[69] The parent CF_3-containing compounds are used to treat an over-expressed enzyme in prostate cancer, aldo-keto reductase 1C3 (AKR1C3). All of the SF_5 derivatives showed good biological selectivities and activities. They will be new potential

drug candidates for prostate cancer due to their high inhibitory potency (IC_{50} < 100 nM) and selectivity for AKR1C3 over AKR1C2 (IC_{50} ratio > 150).

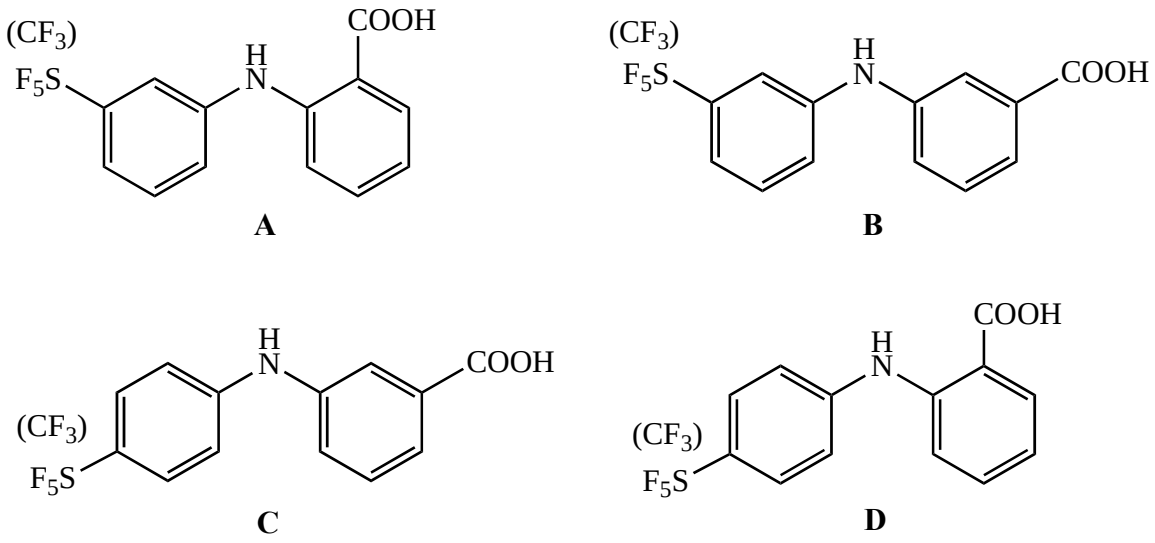


Figure 2-4. *Pentafluorosulfanylated analogues of flufenamic acid.*[69]

2.1.4.3 Applications in Materials Chemistry

The earliest application of pentafluorosulfanyl-containing molecules in materials chemistry was the preparation of liquid crystalline (LCs) materials. LCs have high polarity and lipophilicity, and they are widely used as display materials in common electronic devices, such as computers, smart phones, flat television, etc. The introduction of a SF_5 group into a LC was found to significantly improve its properties by affording a higher density, better thermal stability, and detonation performance.[70] Researchers at Merck KGaA modified widely used fluorinated LC molecules by substitution with a SF_5 group

(**Figure 2-5**).[71] The new SF_5-containing materials have considerable improvement of important parameters of LC materials, such as enhanced dielectric anisotropy and lower birefringence.

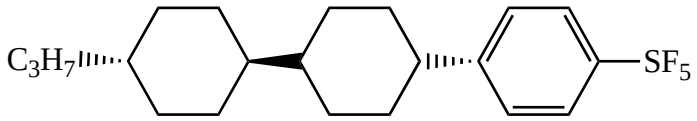


Figure 2-5. *SF_5-containing liquid crystal.*[71]

In 1990, Sitzmann and Thrasher, *et al*. claimed the potential application of SF_5-containing polynitroaliphatic compounds as low melting energetic plasticizers.[72] They prepared SF_5-containing model compounds by condensing polynitroalcohols with pentafluorosulfanylacetic acid, which was generated from the hydrolysis of pentafluorosulfanylacetyl chloride. Tris(2-fluoro-2,2-dinitroethyl)-pentafluorosulfanyl-ethyl orthocarbonate was selected for a more detailed study of its physical properties due to its relatively high melting point and ease of synthesis. The following detonation calorimetry experiments indicated that tris(2-fluoro-2,2-dinitroethyl)-pentafluorosulfanyl-ethyl orthocarbonate had a significantly reduced impact sensitivity relative to the corresponding compound without a SF_5 group.

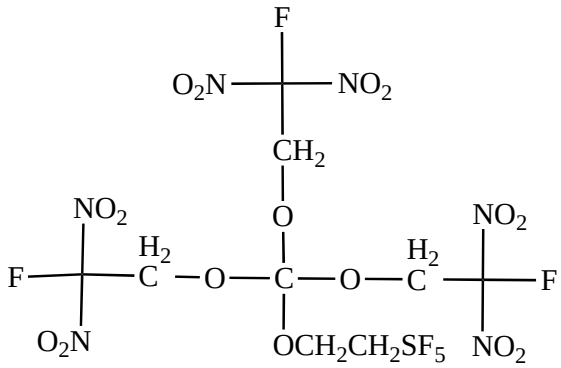


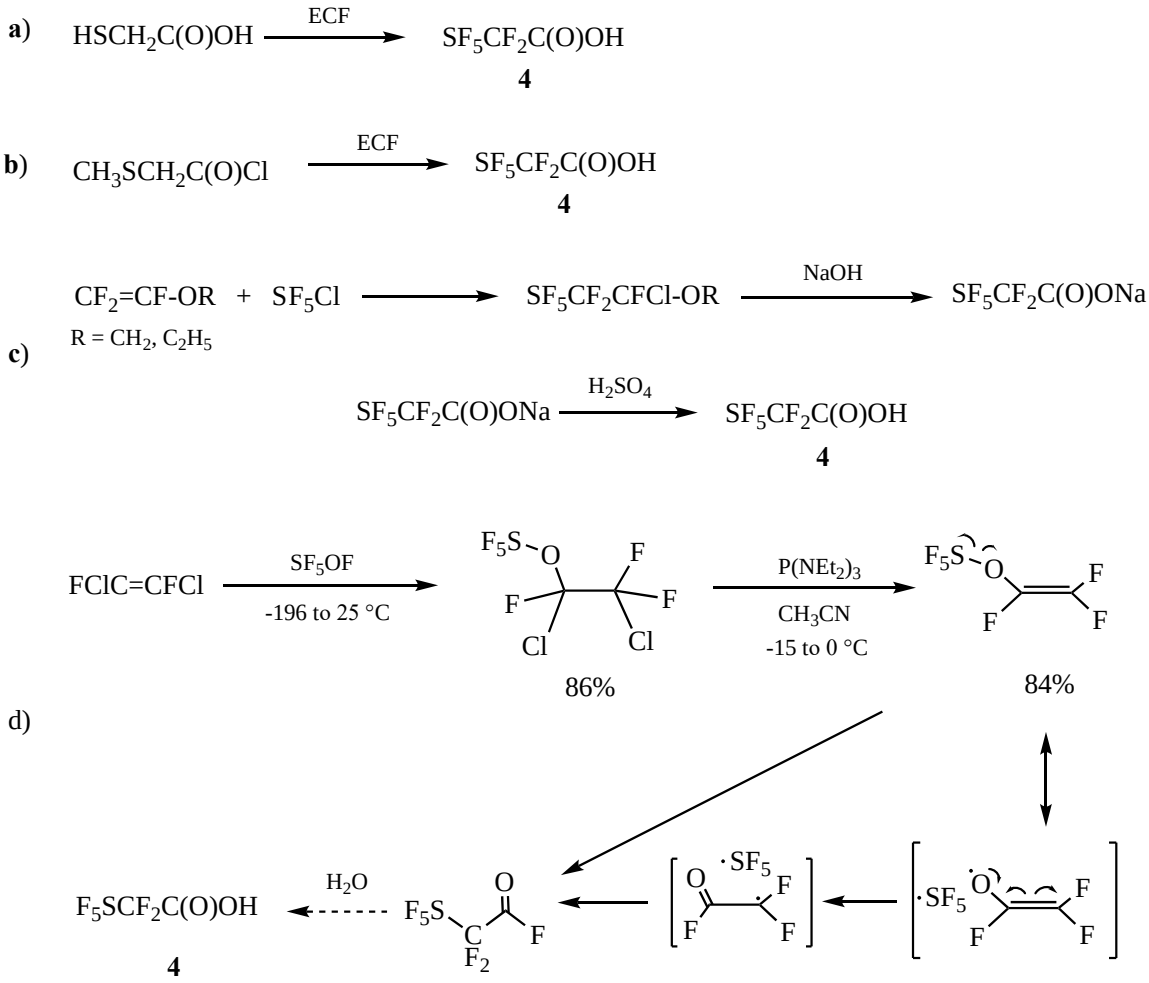
Figure 2-6. *Tris(2-fluoro-2,2-dinitroethyl)-pentafluorsulfanylethyl orthocarbonate.*[72]

2.2 Results and Discussion

2.2.1 Synthesis of Pentafluorosulfanyldifluoroacetic Acid

The improvement on performance of organic compounds containing the pentafluorosulfanyl group has led to a resurgence in the interest in potential applications of these compounds in the areas of agriculture, medical science, and functional materials. However, the development of SF_5 chemistry in the past 60 years has been slow because of the lack of commercially available SF_5 starting materials. The common sources of the SF_5 group, namely SF_5Cl, SF_5Br, and S_2F_{10}, are gases at room temperature, and traditional organic chemists prefer to use liquid and/or solid to investigate the synthesis of novel SF_5-containing molecules or methodological studies. With the considerable continued interest in the development of SF_5 substituent group chemistry, my challenge was to prepare a key starting material for the synthesis of compounds bearing the SF_5CF_2 moiety. Therefore, the molecule pentafluorosulfanyldifluoroacetic acid [$SF_5CF_2C(O)OH$] was chosen as a target for accomplishing this goal.

Pentafluorosulfanyldifluoroacetic acid **4** was first synthesized and introduced to the public in 1956 by Haszeldine and Nyman via electrochemical fluorination of thioglycolic acid or methylsulfanylacetyl chloride, respectively, in low yield (**Scheme 2-18**, Paths a and b).[29] Several years later, Young *et al*. tried to improve Haszeldine's method, but unfortunately, the target compound could not be isolated.[31] In 1970, Dr. Knunyants *et al*. used an alkyltrifluorovinyl ether and pentafluorosulfanyl chloride as starting materials for



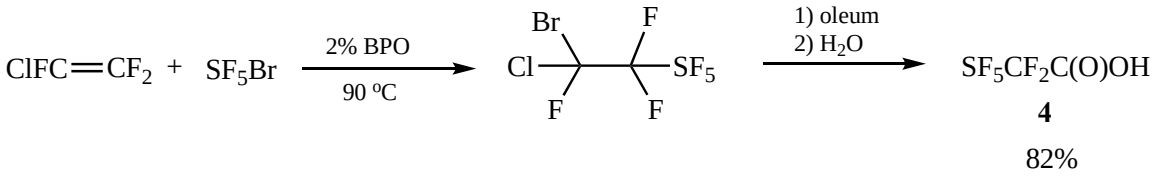
Scheme 2-18. *History of the synthesis of $SF_5CF_2C(O)OH$.*[29,31,73-75]

the preparation of $SF_5CF_2C(O)OH$ via several steps (**Scheme 2-18**, Path c).[73] Compound **4** was prepared in 70% yield after the hydrolysis of the ester. However, this method could not be widely used because of the limited availability of the reagents applied. Furthermore, alkyltrifluorovinyl ethers ($ROCF=CF_2$) are highly reactive compounds, and thus they are easily polymerized at low temperature.[74] In 2007, DesMarteau *et al*. discovered that pentafluorosulfanyltrifluorovinyl ether rearranges to form pentafluorosulfanyldifluoro-acetyl fluoride [$SF_5CF_2C(O)F$] via a radical mechanism at room temperature (**Scheme 2-18**,

Path d).[75] Then the generated $SF_5CF_2C(O)F$ can be easily hydrolyzed to form the desired compound $SF_5CF_2C(O)OH$. Unfortunately, the pentafluorosulfanyloxofluoride used as a starting material is not easily prepared.

Thus, easily scalable and convenient synthetic routes to prepare pentafluoro-sulfanyldifluoroacetic acid **4** were developed by our group.[76] This work was done in collaboration with Andrej V. Matsnev, Mark A. Stanton, and Kyle A. Berger. I carried out the synthetic route to compound **4** based on the reaction of pentafluorosulfanyl bromide with chlorotrifluoroethylene. A mixture of SF_5Br and chlorotrifluoroethylene in the presence of 2% BPO was stirred at 90 °C to give 1-pentafluorosulfanyl-2-bromo-2-chloro-trifluoroethane ($SF_5CF_2CFBrCl$). Oxidation of $SF_5CF_2CFBrCl$ with oleum produced $SF_5CF_2C(O)F$. Finally, hydrolysis of $SF_5CF_2C(O)F$ with H_2O gave the desired compound **4** in high yield (**Scheme 2-19**).

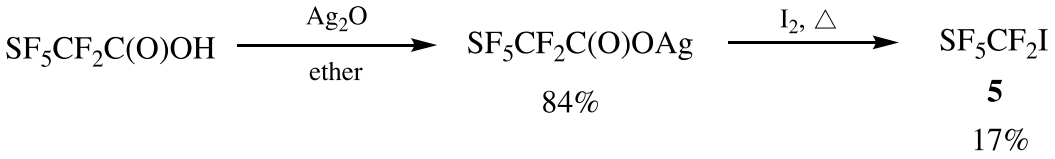
The results were published in *Organic Letters* **2014,** *16*, 2402-2405.



Scheme 2-19. *Preparation of $SF_5CF_2C(O)OH$ from SF_5Br and chlorotrifluoroethylene.*[76]

2.2.2 Synthesis of $SF_5(CF_2)_n$-Containing Halides

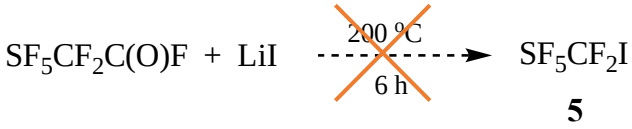
The importance of $TMSCF_3$ as a reagent for the introduction of the trifluoromethyl moiety into a variety of substrates has been discussed in Chapter 1 in the section on trifluoromethylation. Therefore, the anticipated pentafluorosulfanyldifluoromethylene trimethylsilane (SF_5CF_2TMS) with a "super-trifluoromethyl" group would be a very useful SF_5-containing building block, and the synthetic application of this building block would open the door for the development of SF_5 chemistry. Pentafluorosulfanyldifluoro-iodomethane (SF_5CF_2I, **5**) was synthesized as a starting material for the investigation of methods toward the preparation of SF_5CF_2TMS. According to the synthetic route for compound **5** reported by Knunyants *et al.*,[73] a mixture of $SF_5CF_2C(O)OH$ and Ag_2O (1.0-equiv.) in ether produces silver pentafluorosulfanyldifluoroacetate [$SF_5CF_2C(O)OAg$] in 84% yield. Then the reaction of $SF_5CF_2C(O)OAg$ with anhydrous iodine at 220 °C produces compound **5** in 20% yield (**Scheme 2-20**). Because of the high reaction temperature used in step 2, some of the SF_5CF_2I undergoes decomposition, and the overall yield is very low (17%).



Scheme 2-20. *Synthesis of SF_5CF_2I.*[73]

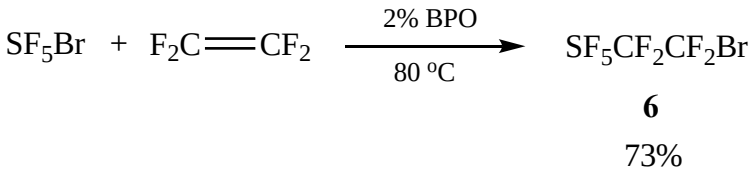
The reaction of $SF_5CF_2C(O)F$ with lithium iodide at 200 °C in a stainless cylinder was applied to find an alternative synthesis route to prepare compound **5**. This method is a

one-step reaction and lower reaction temperature (**Scheme 2-21**). However, no reaction was observed.



Scheme 2-21. *Attempted preparation of SF_5CF_2I from $SF_5CF_2C(O)F$ and LiI.*

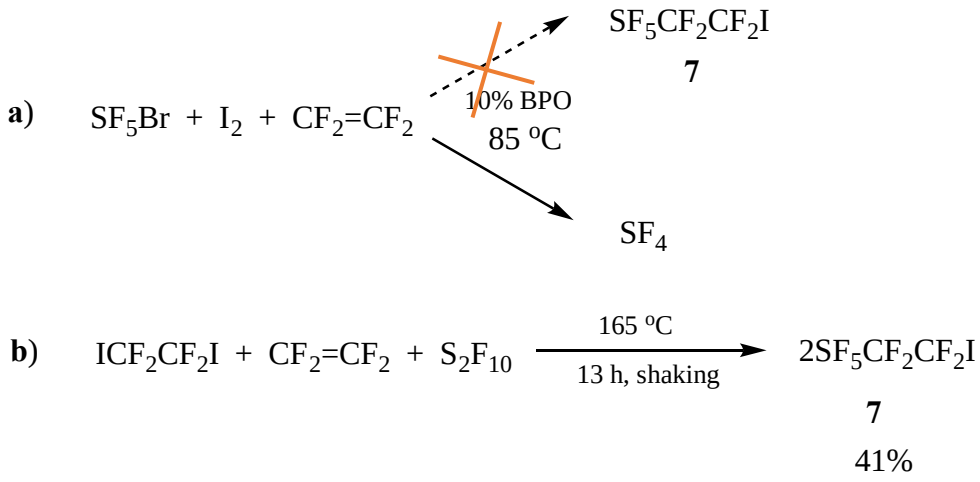
Unfortunately, SF_5CF_2I is highly volatile and light sensitive. Thus, I turned my attention to exploring the synthetic route to pentafluorosulfanyltetrafluoroethyl-trimethylsilane ($SF_5CF_2CF_2TMS$) from $SF_5CF_2CF_2Br$ **(6)**, the latter of which is much more stable and easier to handle. According to Gard's synthetic route, compound **6** can be easily prepared in 73% yield from the reaction of SF_5Br with TFE in the presence of 2% BPO (**Scheme 2-22**).[77]



Scheme 2-22. *Synthesis of $SF_5CF_2CF_2Br$.*[77]

The more reactive pentafluorosulfanyltetrafluoroethyl iodide ($SF_5CF_2CF_2I$, **7**) was also prepared in order to study its application in SF_5-containing compounds. Initially, the radical addition reaction of SF_5Br, I_2, and TFE in the presence of 10% BPO failed to give compound **7**, and only SF_4 was observed as a decomposition product (**Scheme 2-23**, Path a). Compound **7** was originally prepared from S_2F_{10} in low yield by Gard *et al*.[78-79] He claimed that lots of toxic starting materials were not converted under his reaction conditions. I modified Gard's reaction conditions[78-79] by increasing both reaction

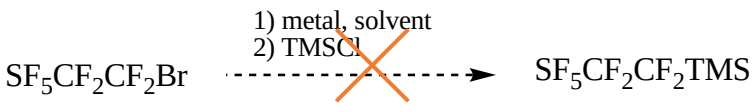
temperature and time. The staring materials (ICF_2CF_2I, $CF_2=CF_2$ and S_2F_{10}) were totally converted into compound **7**. But the desired product **7** was isolated only in 41% yield because of the decomposition of compound **7** during its the distillation (**Scheme 2-23**, Path b).



Scheme 2-23. *Synthesis of $SF_5CF_2CF_2I$.*[78-79]

2.2.3 Synthesis of $SF_5CF_2CF_2TMS$ from $SF_5CF_2CF_2X$ (X = Br, I)

Zinc (Zn), magnesium (Mg), and aluminum (Al) have been used in the preparation of $TMSCF_3$ from CF_3Br.[80] Therefore, all of these metals were investigated for the preparation of $SF_5CF_2CF_2TMS$ from $SF_5CF_2CF_2Br$ (**Scheme 2-24**).



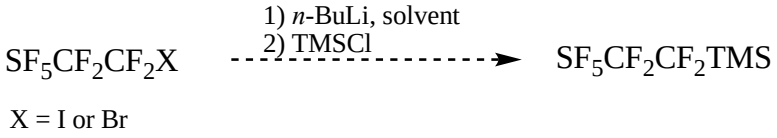
Scheme 2-24. *Attempted preparation of $SF_5CF_2CF_2TMS$ using $SF_5CF_2CF_2Br$ and metal.*

However, the reaction of $SF_5CF_2CF_2Br$ with metal and TMSCl under a number of reaction conditions failed to give the desired product $SF_5CF_2CF_2TMS$ (**Table 2-3**).

Table 2-3. *Attempted preparation of $SF_5CF_2CF_2TMS$ from $SF_5CF_2CF_2Br$ and metal*

	Metal	$SF_5CF_2CF_2Br$/Metal/TMSCl	Solvent	T (°C)	Result
1	Zn	2.5/1.0/1.4	NMP	r.t.	Decomposition
2	Al	1.5/1.0/1.5	NMP	0 - r.t.	Decomposition
3	Zn	2.7/1.0/4.0	Diglyme	r.t.	No reaction
4	Mg	2.5/1.0/4.0	Diglyme	r.t.	No reaction
5	Mg	2.5/1.0/4.0	THF	r.t.	Decomposition
6	Mg	1.1/1.0/1.0	THF	0	No reaction
7	$MgBr_2 \cdot OEt_2$	1.0/1.3/1.3	THF	0	No reaction

Next, treatment of $SF_5CF_2CF_2X$ (X: Br, I) with a lithium reagent followed by addition of TMSCl at low temperature was studied for the preparation of $SF_5CF_2CF_2TMS$ (**Scheme 2-25**).



Scheme 2-25. *Attempted preparation of $SF_5CF_2CF_2TMS$ using $SF_5CF_2CF_2$-halide and organic reagents.*

As shown in **Table 2-4**, the reaction of $SF_5CF_2CF_2Br$ with *n*-BuLi followed by the addition of TMSCl was carried out in heptane at -83 °C (entry 1). A ^{19}F NMR spectrum of

the reaction mixture showed that the desired product $SF_5CF_2CF_2TMS$ was formed in very low yield along with large amounts of TMSF and LiF, but the $SF_5CF_2CF_2Br$ was not completely converted (**Figure 2-7**) The solvent and reaction temperature were changed in an effort to improve the yield of $SF_5CF_2CF_2TMS$. However, the yield of $SF_5CF_2CF_2TMS$ did not increased under any of the reaction conditions (entries 2-5). Then the use of the more reactive iodo compound $SF_5CF_2CF_2I$, instead of $SF_5CF_2CF_2Br$, was investigated for synthesis of $SF_5CF_2CF_2TMS$. However, the yield of the desired product was still not improved upon (entries 6-8).

Table 2-4. *Attempted preparation of $SF_5CF_2CF_2TMS$ using $SF_5CF_2CF_2$-halides and organolithium reagents*

	$SF_5CF_2CF_2X$	Base	TMSCl (eq.)	Solvent	*T* (°C)	Result
1	$SF_5CF_2CF_2Br$	*n*-BuLi	1.2	Heptane	-83	Trace
2	$SF_5CF_2CF_2Br$	*n*-BuLi	1.2	THF	-80	No reaction
3	$SF_5CF_2CF_2Br$	*n*-BuLi	1.2	Hexane	-80	Trace
4	$SF_5CF_2CF_2Br$	*n*-BuLi	1.2	Heptane	-100	Trace
5	$SF_5CF_2CF_2Br$	*n*-BuLi	1.2	Et_2O	-100	No reaction
6	$SF_5CF_2CF_2I$	*n*-BuLi	1.2	THF	-90	No reaction
7	$SF_5CF_2CF_2I$	*n*-BuLi	1.2	Heptane	-76	Trace
8	$SF_5CF_2CF_2I$	*n*-BuLi	2.2	THF	-76	No reaction

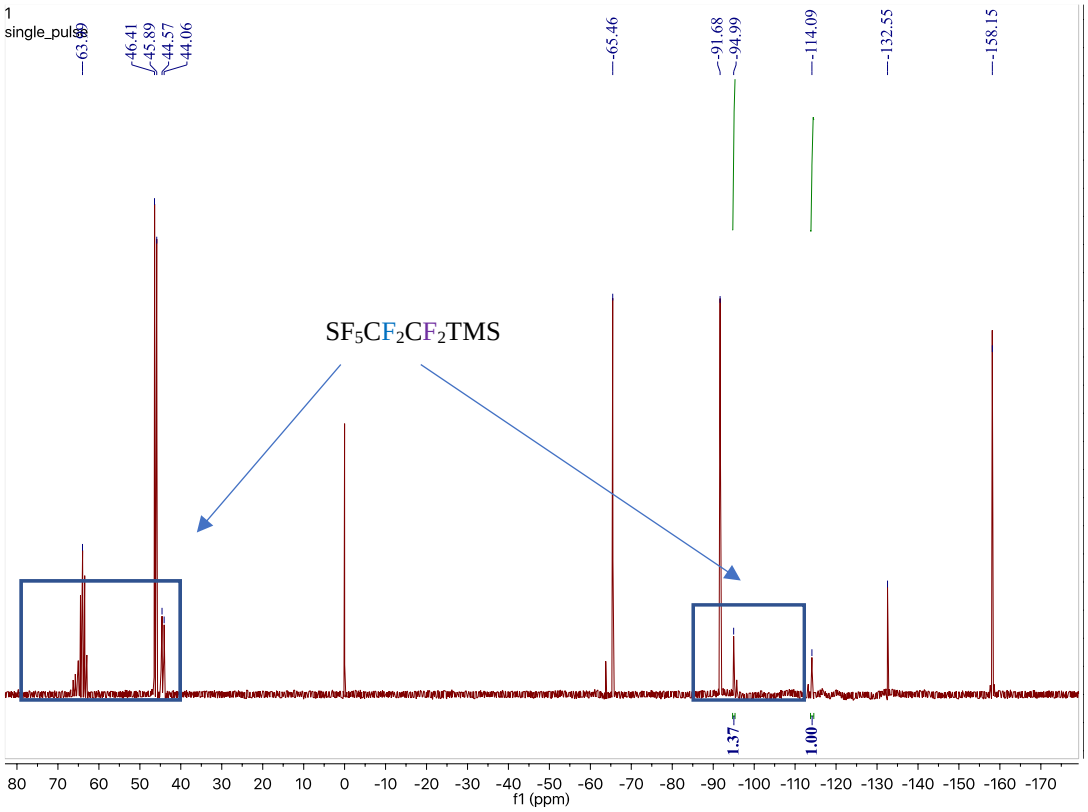
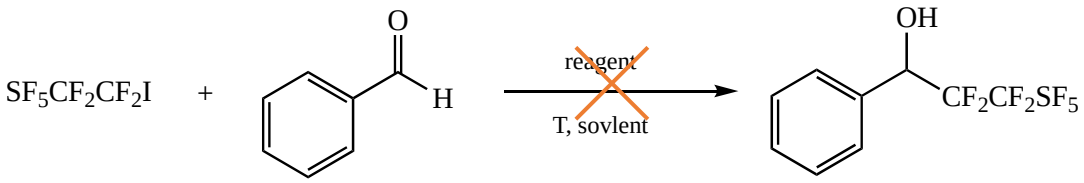


Figure 2-7. *^{19}F NMR spectrum of the reaction mixture from the preparation of $SF_5CF_2CF_2TMS$.*

2.2.4 Attempted Preparation of a $SF_5CF_2CF_2$-Containing Alcohol from Organic Substrates

The reaction of $SF_5CF_2CF_2I$ with an aldehyde in the presence of a metal was investigated in an effort to prepare a $SF_5CF_2CF_2$-containing alcohol (**Scheme 2-26**). Because DMF can stabilize the CF_3 anion, DMF was first chosen as the solvent. The reaction of $SF_5CF_2CF_2I$ with benzaldehyde in the presence of zinc in DMF at room temperature failed to give a $SF_5CF_2CF_2$-containing alcohol (**Table 2-5,** entry 1). When

THF was used as solvent instead of DMF, the desired product was also not formed (entry 2). In addition, treatment of $SF_5CF_2CF_2I$ with *n*-BuLi in THF at -78 °C followed by addition of benzaldehyde also failed to give a $SF_5CF_2CF_2$-containing alcohol (entry 3).



Scheme 2-26. *Attempted preparation of a $SF_5CF_2CF_2$-containing alcohol using an aldehyde and $SF_5CF_2CF_2I$.*

Table 2-5. *Attempted preparation of a $SF_5CF_2CF_2$-containing alcohol using an aldehyde and $SF_5CF_2CF_2I$*

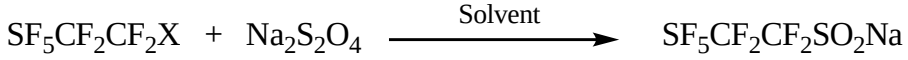
	Reagent	Benzaldehyde (eq.)	Solvent	T (°C)	Result
1	Zn (2 eq.)	1.1	DMF	r.t.	Decomposition
2	Zn (2 eq.)	1.1	THF	r.t.	Decomposition
3	*n*-BuLi (1.1 eq.)	1.1	THF	-78	Decomposition

2.2.5 Attempted Preparation of $SF_5CF_2CF_2SO_2Na$ from $SF_5CF_2CF_2X$ (X = Br, I)

In 1981, W.-Y. Huang discovered a convenient and practical procedure for the synthesis of $R_fCF_2SO_2Na$ from the reaction of R_fCF_2X (X: Br, I) with $Na_2S_2O_4$. More recently, this process has been called the sulfinatodehalogenation reaction.[81] With $SF_5CF_2CF_2I$ and $SF_5CF_2CF_2Br$ in hand, the sulfinatodehalogenation reaction of these two

$SF_5CF_2CF_2$-containing halides was explored. Unfortunately, $SF_5CF_2CF_2SO_2Na$ was not formed from the either $SF_5CF_2CF_2I$ or $SF_5CF_2CF_2Br$ under a variety of conditions that were tried (**Table 2-6**).

Table 2-6. *Attempted application of $SF_5CF_2CF_2$-halide in the sulfinatodehalogenation reaction*

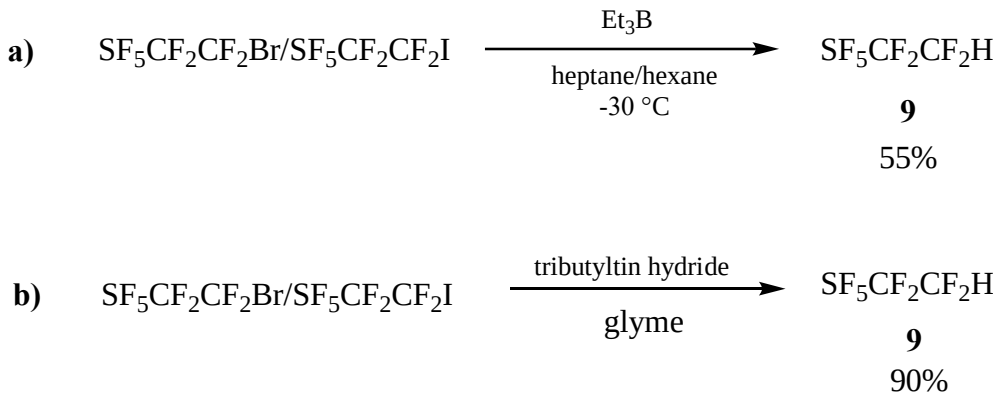


	$SF_5CF_2CF_2X$ (A)	SO_3^{2-} source (B)	A/B (ratio)	Solvent	*T* (°C)	Result
1	$SF_5CF_2CF_2Br$	$Na_2S_2O_4$	1/4	DMSO	r.t.	Decomposition
2	$SF_5CF_2CF_2Br$	$Na_2S_2O_4$	1/4	CH_3CN/H_2O (3/1)	r.t.	Decomposition
3	$SF_5CF_2CF_2Br$	$Na_2S_2O_4$	1/2	DMF/H_2O (2/1)	80	Decomposition
4	$SF_5CF_2CF_2I$	$Na_2S_2O_4$	1/1.3	$Diglyme/H_2O$ (1.5/1)	r.t.	No reaction
5	$SF_5CF_2CF_2I$	$Na_2S_2O_4/NaHCO_3$	1/1.3	$Diglyme/H_2O$ (1.5/1)	r.t.	No reaction
6	$SF_5CF_2CF_2I$	$Na_2S_2O_4/NaHCO_3$	1/1.3	$EtOH/H_2O$ (3/1)	r.t.	No reaction
7	$SF_5CF_2CF_2I$	$Na_2S_2O_4/NaHCO_3$	1/1.3	CH_3CN/H_2O (3/1)	r.t.	Decomposition

2.2.6 Synthesis of Pentafluorosulfanyltetrafluoroethane from $SF_5CF_2CF_2X$ (X = Br, I)

Pentafluorosulfanyltetrafluoroethane ($SF_5CF_2CF_2H$, **9**) was first synthesized and reported by Baba *et al*. from the electrochemical fluorination of ethanethiol.[82] Two new procedures were developed for the synthesis of compound **9**. The reaction of $SF_5CF_2CF_2Br$ or $SF_5CF_2CF_2I$ with Et_3B in heptane/hexane at -30 °C gave $SF_5CF_2CF_2H$ in 55% yield

(**Scheme 2-27**, Path a). However, compound **9** was hard to isolate from the reaction mixture due to the close melting points of $SF_5CF_2CF_2H$ and hexane. The yield of compound **9** was improved to 90% by treatment of $SF_5CF_2CF_2Br$ or $SF_5CF_2CF_2I$ with tributyltin hydride in glyme (**Scheme 2-27**, Path b).

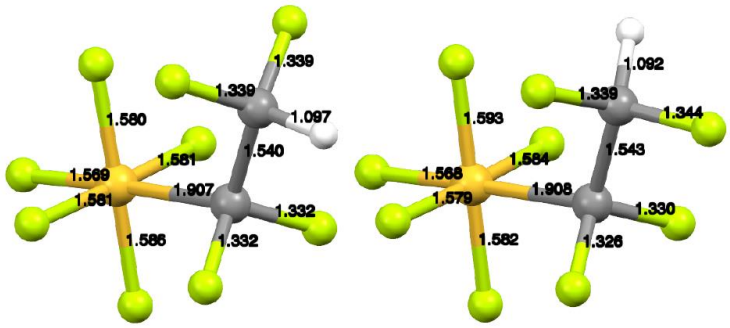


Scheme 2-27. *Synthesis of pentafluorosulfanyltetrafluoroethane.*

The infrared spectra for compound **9** has the characteristic absorption bands of a SF_5 group. A compound containing a SF_5 group normally has the most intense band in the region of 832-885 cm^{-1} (S-F stretching modes) and in the region of 600 cm^{-1} (S-F deformation modes).[58] In compound **9**, these stretching absorption bands are found in the 808-878 cm^{-1} region, while the deformation bands are located in the 560-610 cm^{-1} region. The strong C-F absorption bands are found in the 1140-1400 cm^{-1} region. In addition, the medium C-H absorption band is found at 3018 cm^{-1}. Furthermore, Dr. Christian Mück-Lichtenfeld and Dr. Günter Haufe have accomplished the computational calculation of the molecular geometry and harmonic vibrational frequencies of compound **9**, the calculation was processed by DFT methods with a PBE0-D3/def2-TZVP (hybrid functional with dispersion correction) basis set (**Table 2-7** and **Figure 2-8**). According to the

computational studies, configuration B has a lower energy and thus is more stable than configuration A. Furthermore, the harmonic vibration frequencies of configuration B for compound **9** match the experimental IR spectrum of compound **9** much better than do the vibration frequencies calculated for configuration A.

The -CF_2H group of compound **9** appears as doublet of multiplets (-135.2 ppm, $^2J_{F,H}$ = 52.0 Hz) in the ^{19}F NMR spectrum. On the other hand, the ^1H NMR spectrum gives a triplet of triplets for the -CF_2H group (6.1 ppm, $^2J_{H,F}$ = 51.0 Hz, $^3J_{H,F}$ = 6.0 Hz).



4 (Conf. A)
ΔG_{rel} = +0.5 kcal/mol

4 (Conf. B)
ΔG_{rel} = +0.0 kcal/mol

Figure 2-8. *Geometry optimization of $SF_5CF_2CF_2H$ with PBE0-D3/def2-TZVP (hybrid functional with dispersion correction).*

Table 2-7. *Harmonic vibrational frequencies (in cm^{-1}) of $SF_5CF_2CF_2H$*

Mode	7	8	9	10	11	12	13	14	15	16	17
Conf. A	31.38	110.15	156.53	206.43	208.90	232.14	310.87	326.19	344.08	371.28	409.40
Intensity (%)	0.00	0.44	0.09	0.36	0.37	0	0.31	0.12	0.05	0.21	1.69
Conf. B	34.50	97.57	154.36	206.50	226.09	260.10	282.92	321.68	334.92	358.38	403.50
Intensity (%)	0.02	0.23	0.24	0.39	0.10	0.36	1.02	0.05	0.32	0.21	0.49
Expt.											
Intensity (%)											

Table 2-7. *Harmonic vibrational frequencies (in cm^{-1}) of $SF_5CF_2CF_2H$ (continued)*

Mode	18	19	20	21	22	23	24	25	26	27	28
Conf. A	416.03	493.54	526.07	558.00	568.72	580.76	586.67	625.11	632.54	690.98	698.46
Intensity (%)	0.23	0.00	0.18	17.91	8.81	2.93	21.08	0.09	0.98	0.73	5.77
Conf. B	420.42	469.57	490.18	560.09	575.62	582.37	607.86	620.81	640.87	685.74	819.98
Intensity (%)	0.29	0.50	0.00	6.15	2.23	2.67	13.73	0.35	1.17	2.95	59.50
Expt.	418.75			561.55		584.77	607.50			684.76	808.78
Intensity (%)	1.00			36.00		12.00	58.00			17.50	98.00

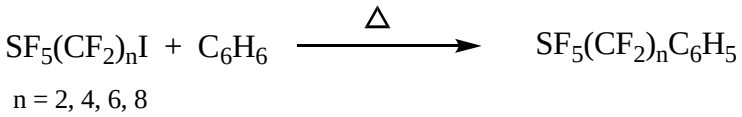
Table 2-7. *Harmonic vibrational frequencies (in cm^{-1}) of $SF_5CF_2CF_2H$ (continued)*

Mode	29	30	31	32	33	34	35	36	37	38	39
Conf. A	887.64	911.06	912.69	1125.08	1180.67	1189.41	1237.29	1251.06	1378.26	1420.63	3075.80
Intensity (%)	98.11	100.00	93.61	0.06	75.42	31.24	96.31	0.97	3.51	9.71	5.23
Conf. B	886.92	903.22	912.38	1035.07	1164.43	1179.09	1234.94	1297.47	1378.75	1418.18	3127.32
Intensity (%)	64.51	100.00	91.92	2.84	21.95	34.07	63.65	37.90	2.21	5.28	3.10
Expt.	877.10			1025.75	1149.22		1202.01	1267.09	1361.22	1418.92	3017.61
Intensity (%)	100.00			22.00	98.00		98.00	88.00	6.00	38.00	28.00

2.2.7 Synthesis of Pentafluorosulfanyltetrafluoroethylated Fullerene

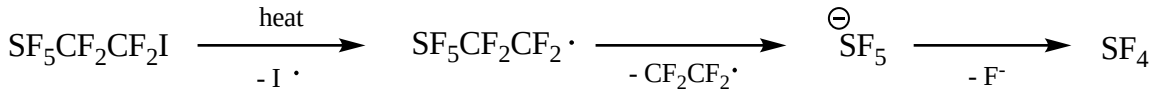
The synthetic chemistry of fullerenes is a vibrant, rapidly developing field of research.[83] All-carbon cages are fascinating chemical substrates that allow for multitudes of chemical reactions to be applied: from cycloadditions, to radical reactions, polymerizations, and others. The chemical derivatization of fullerenes results in convenient and effective modification of their physical and chemical properties. When electron-withdrawing groups are added to fullerene structures, their electron accepting properties are enhanced. Fullerene acceptors have become prototypical, and they are some of the best performing materials in organic optoelectronic devices, such as organic photovoltaics. A series of trifluoromethyl-containing fullerenes have been prepared and studied by the research group of Strauss and Boltalina at the Colorado State University (CSU).[84] However, a fullerene bearing a "super trifluoromethyl group," namely the pentafluorosulfanyl group, has never been prepared or reported. The SF_5 group has been considered as a more electron-withdrawing group than the CF_3 group, and its presence may further change the polarizability, resonance, and inductive effects of the substrate. Therefore, in this collaborative research work with the group of Strauss and Boltalina at CSU, I succeeded in preparing the first SF_5-containing fullerene derivatives with the direct addition of the bulky $SF_5CF_2CF_2$ group starting from $SF_5CF_2CF_2I$.

In 2001, Gard reported the first examples of the addition of a SF_5-containing *n*-perfluoroalkyl group to benzene derivatives (**Scheme 2-28**).[85] Benzene was used as both the solvent and the substrate to provide SF_5-containing *n*-perfluoroalkyl benzene derivatives in 39-55% yields. However, Gard's procedure was not suitable for the preparation of SF_5-containing fullerene derivatives. Fullerenes are solids and have poor solubility in common organic solvent, and furthermore, the amount of C_{60} or C_{70} should be limited due to their high cost and difficulty in being purified. Meanwhile, due to the high molecular weight of the $SF_5CF_2CF_2$ group, I focused on the selective synthesis of the *bis*-addition product, especially after some initial feedback from the CSU group on our first samples.



Scheme 2-28. *Gard's synthesis of SF_5-containing n-perfluoroalkyl benzene derivatives.*[85]

In our initial investigation, the generated $SF_5CF_2CF_2\cdot$ radical was not stable under the conditions attempted for the thermal addition, and the radical decomposed to give SF_4 as the main product. The decomposition may be due to the fact that the bulky SF_5 group acts as a leaving group to generate the SF_5^- anion from the $SF_5CF_2CF_2\cdot$ radical. Then the SF_5^- anion decomposes to form the more stable SF_4 and F^- (**Scheme 2-29** and **Figure 2-9**). Copper (Cu) powder was applied to stabilize the $SF_5CF_2CF_2\cdot$ radical and absorb the *in-situ* generated iodine radical, which could also simplify the purification process in that much of the volatile iodine would be converted to copper(I) iodide (CuI).



Scheme 2-29. *Decomposition of the $SF_5CF_2CF_2$ radical.*

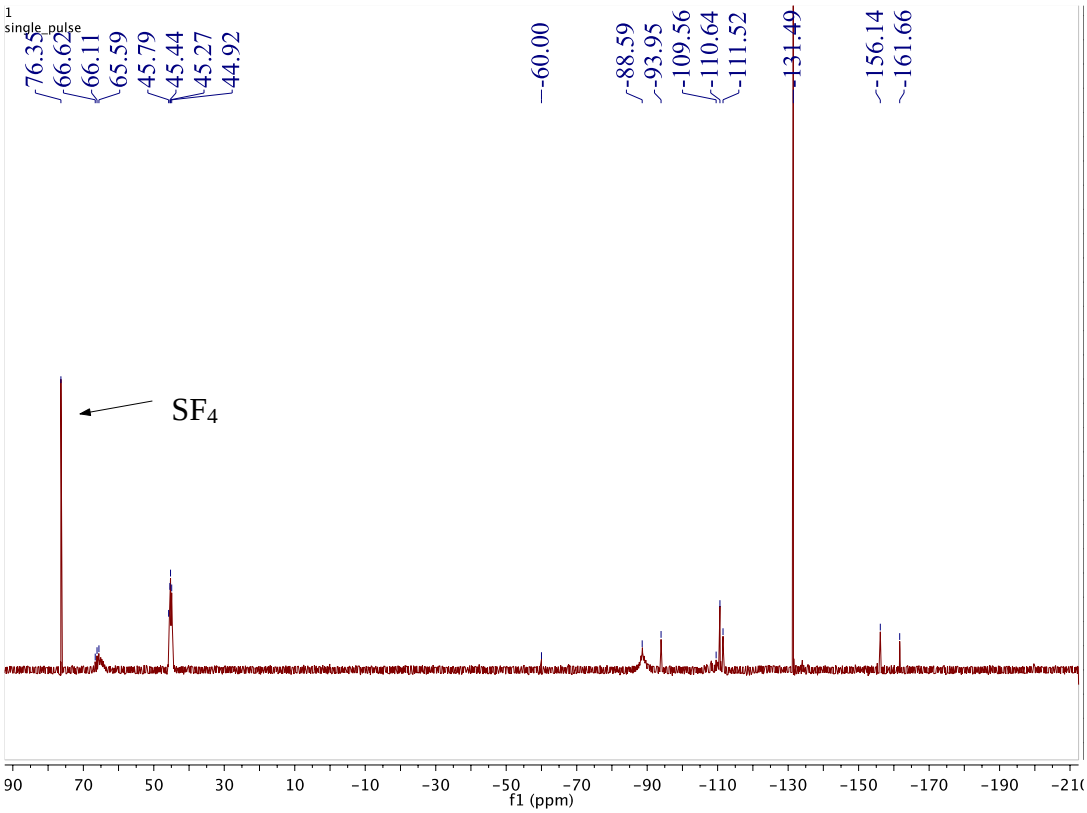


Figure 2-9. *The formation of SF_4 during the reaction of $SF_5CF_2CF_2I$ with C_{60}/C_{70}.*

As shown in **Scheme 2-30**, a 1,2-dichlorobenzene (*o*-DCB) solution containing a fullerene C_{60}/C_{70} mixture and $SF_5CF_2CF_2I$ was heated in the presence of Cu powder to find the optimized reaction conditions. Reaction conditions were varied (amounts of solvent and $SF_5CF_2CF_2I$ used, reaction temperture, heating period) in order to reach the selective generation of a *bis*-pentafluorosulfanyltetrafluoroethylated fullerene as shown in **Table 2-8**. It is a remarkable fact that the lower reaction temperaure is the key to reducing the

formation of by-products (**Figure 2-10**), but reaction temperatures lower than 145 °C give very low conversions of $SF_5CF_2CF_2I$. By ^{19}F NMR spectroscopy, it was shown that 84% of the $SF_5CF_2CF_2I$ was consumed after 3 days of heating at 140 °C. An HPLC-MS study of crude samples indicated that the lower concentration of reactants in *o*-DCB can further improve the selective formation of the *bis*-addition product.

$$C_{60}/C_{70} + mSF_5CF_2CF_2I \xrightarrow{130\text{-}190\ ^oC} (SF_5CF_2CF_2)n\text{-}C_{60}/C_{70}$$

m = 4 or 6

Scheme 2-30. *Optimization of the reaction conditions for the synthesis of $(SF_5CF_2CF_2)_n$-C_{60}/C_{70}.*

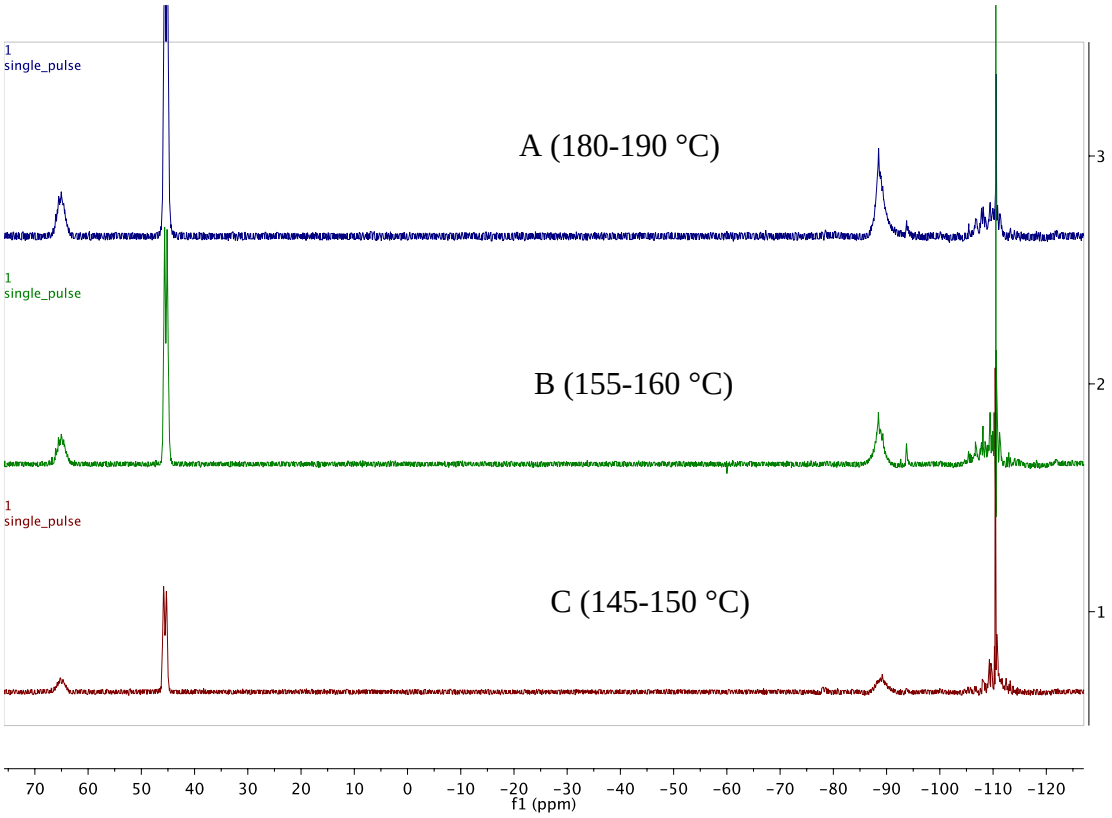


Figure 2-10. *Effect of reaction temperature on the selectivity of the reaction of $SF_5CF_2CF_2I$ with C_{60}/C_{70}.*

Table 2-8. *Optimization of reaction conditions for synthesis of $(SF_5CF_2CF_2)_n$-C_{60}/C_{70}*

	Amount of *o*-DCB (mL)	$SF_5CF_2CF_2I$ (equiv.)	Reaction Temperature (°C)	Reaction Time (hour)
1	1.87	6	190	72
2	3.74	6	155	72
3	3.74	6	145	72
4	6.00	6	145	72
5	4.87	6	145	72
6	3.74	4	145	72
7	3.74	6	145	48
8	3.74	4	135	72
9	6.00	4	140	72

Further HPLC purification and MS studies indicated that the optimal reaction conditions for the formation of *bis*-$(SF_5CF_2CF_2)_2$-C_{60} should be: 3.1 mg/mL of C_{60} in *o*-DCB reacting with four equivalents of $SF_5CF_2CF_2I$ in the presence of Cu at 140 °C for 72 hours (**Scheme 2-31**). HPLC chromatograms of the crude reaction mixture are shown in **Figure 2-11**, where the left trace shows a poor separation of C_{60} derivatives in toluene.

$$C_{60} + 4\ SF_5CF_2CF_2I \xrightarrow[72\ h,\ shaking]{140\ ^oC} (SF_5CF_2CF_2)_2\text{-}C_{60}$$

Scheme 2-31. *Synthesis of $(SF_5CF_2CF_2)_2$-C_{60}.*

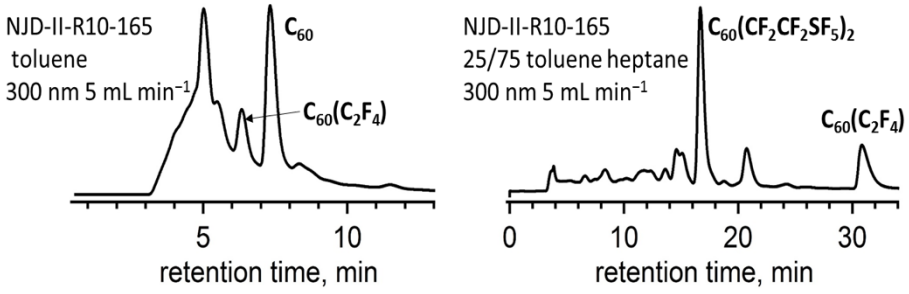


Figure 2-11. *HPLC chromatograms of the crude reaction mixture.*

An improved separation is achieved by using toluene/heptane (25/75) as the mobile phase. The main products are *bis*-$(SF_5CF_2CF_2)_2$-C_{60} and $C_{60}(C_2F_4)$. Mass spectrometry analysis showed an exceptional ability of 1,7-$C_{60}(SF_5CF_2CF_2)_2$ **8** to form adduct ions with eluents [when compared to other 1,7-$C_{60}(R_F)_2$ compounds] leading to more complex mass spectra than expected (**Figure 2-12**). The largest peak at 1174 m/z, corresponds to the molecular ion and ions with larger m/z correspond to adducts with solvent. The collaborators at Colorado State University have been able to grow a single crystal of 1,7-$(SF_5CF_2CF_2)_2$-C_{60}. Unfortunately, the generated crystal did not diffract enough for a structure determination even when using a synchrotron X-ray source at a National Lab. Further study is processing, such as preparing adducts of the product in order to lower the symmetry, etc.

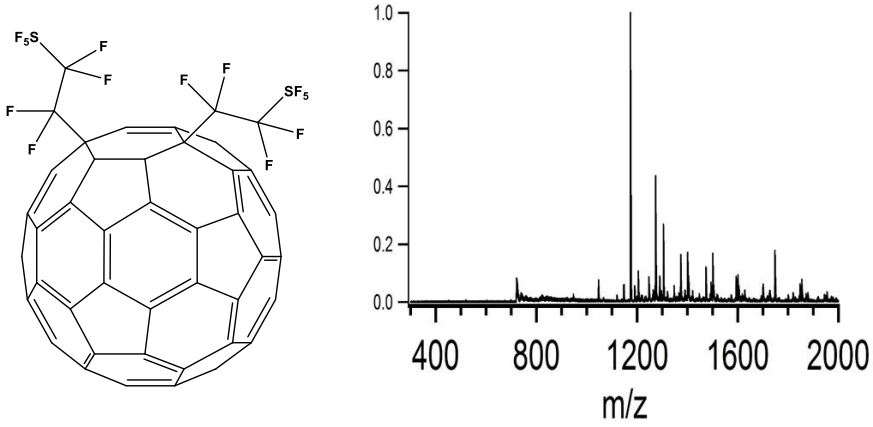


Figure 2-12. *Mass spectral analysis of 1,7-$(SF_5CF_2CF_2)_2$-C_{60}.*

2.2.8 Halogen Bonding of Pentafluorosulfanyl-Containing Perfluoro-alkylated Halides

In 1863, Guthrie *et al*. first reported the original idea of halogen bonding,[86] and Hassel *et al*. used X-ray crystallography to prove the existence of this non-covalent

interaction between a Lewis base and a halogen atom.[87] From then on, halogen bonding has been considered to have great promise for applications in supramolecular chemistry, materials science, biological recognition, drug design, etc.[88] Trifluoromethyl-containing haloperfluoroalkanes are examples of a common class of electron acceptor in halogen bonding.

It was thought that organic molecules modified with a SF_5 functional group may also form halogen bonding due to its more bulky, lipophilic, electron-withdrawing, and chemically inert properties (**Figure 2-13**). Therefore, the formation of halogen bonding from either $SF_5CF_2CF_2Br$ or SF_5CF_2I with various Lewis bases in THF was investigated. However, it was found that the mixtures of a Lewis base and SF_5CF_2I (or $SF_5CF_2CF_2Br$) were unstable in THF. The SF_5-containing perfluoroalkyl halides decomposed, and then the HF generated quickly reacted with the glass of the NMR tubes being used for the studies. Thus $2[C_5H_7N_2]^+[SiF_6]^{2-}$ was formed from a mixture of $SF_5CF_2CF_2Br$ and 2-methyl-pyrazine in THF, and the structure of this complex was determined by X-ray crystallography of the formed crystal (**Figure 2-14**).

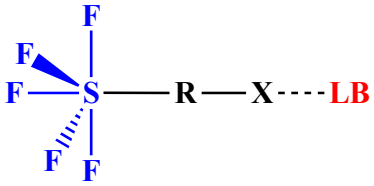


Figure 2-13. *Halogen bonding with SF_5-containing perfluoroalkyl halide.*

After further investigation, SF_5-containing perfluoroalkyl halides were found to be much more stable in an inert and nonpolar solvent, such as pentane. The ^{19}F NMR spectroscopic studies of the halogen bonding between halo-perfluorocarbons and Lewis

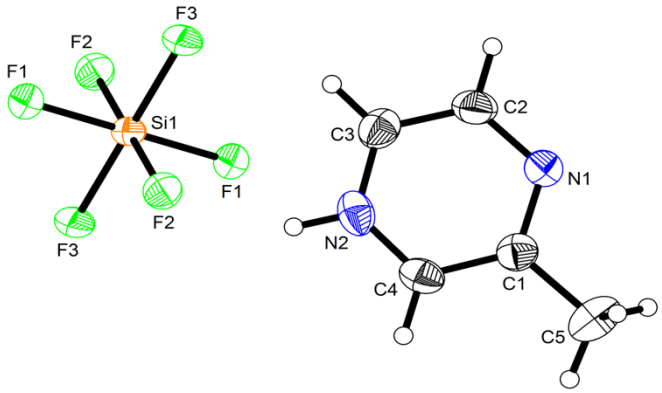


Figure 2-14. *X-ray structure of generated* $2[C_5H_7N_2]^+[SiF_6]^{2-}$.

bases in solution phase have been previously reported by Metrangolo and Hawthorne, *et al*.[89-90] Thus, changes in the ^{19}F NMR chemical shifts of fluorine atoms with the addition of Lewis bases in pentane was used to determine the halogen bonding effect. For example, changes in the chemical shift of the $BrCF_2$- fluorine atoms in $SF_5CF_2CF_2Br$ were found to be smaller than 0.05 ppm in the presence of 26.6 equivalents of 2-methylpyrazine (**Table 2-9**). In the case of a stronger Lewis base piperidine, the changes in the chemical shift of the $BrCF_2$- fluorine atoms in $SF_5CF_2CF_2Br$ reached to 0.26 ppm (**Table 2-10**). Enhancement of the halogen bonding effect in $SF_5CF_2CF_2Br$ with stronger Lewis bases is also shown in **Figure 2-15**. For example, it was found that the ^{19}F chemical shift of the ICF_2- fluorine atoms in SF_5CF_2I in pentane in the presence of piperidine was dramatically changed. When SF_5CF_2I was mixed with one equivalent of piperdine in pentane, the change of chemical shift of the ICF_2- fluorine atoms in SF_5CF_2I was 4.11 ppm, and this change increased to 10.79 ppm when nine equivalents of piperidine were used (**Table 2-11**). The experimental results gave evidence that much stronger halogen bonding occurred between SF_5CF_2I and Lewis bases than that observed with $SF_5CF_2CF_2Br$ (**Figure 2-16**).

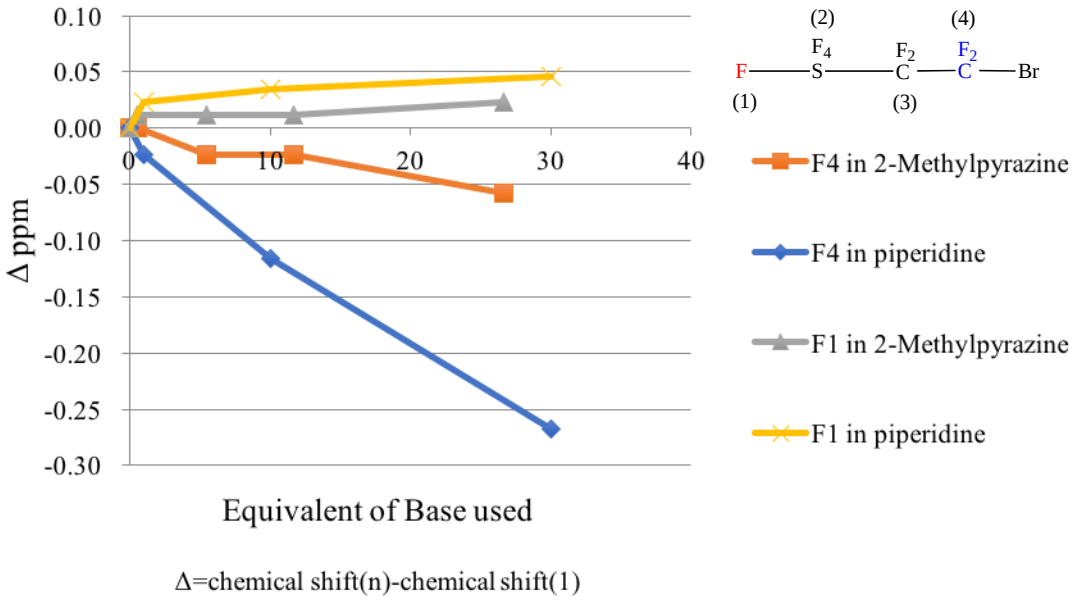


Figure 2-15. *Halogen bonding effects from $SF_5CF_2CF_2Br$ with Lewis base in pentane.*

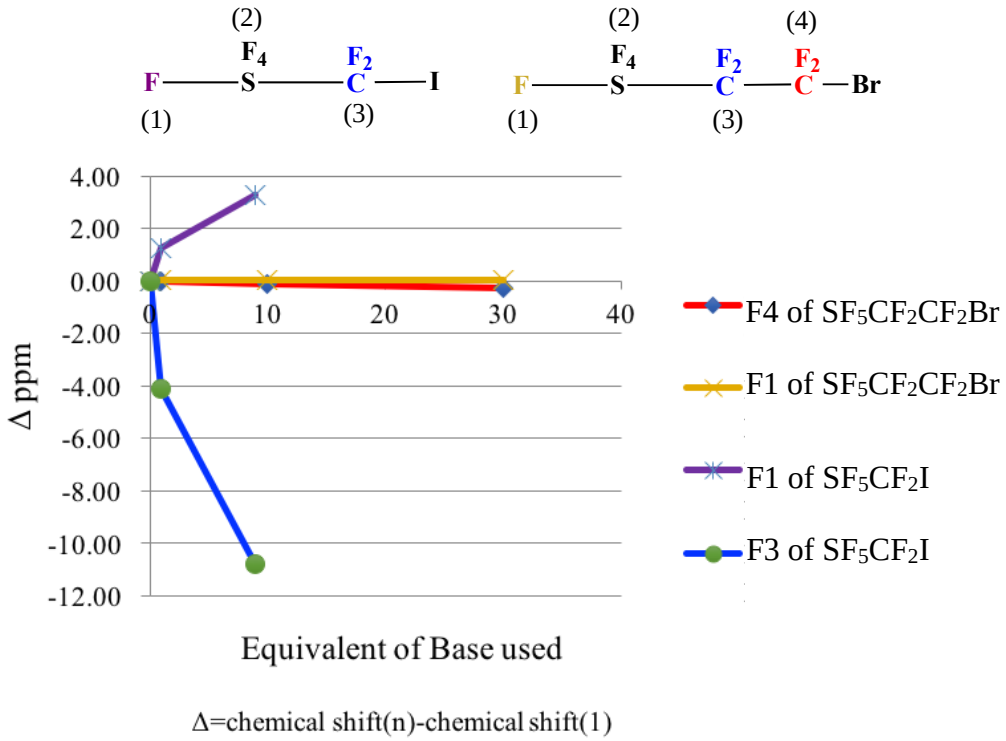


Figure 2-16. *Comparison of the halogen bonding effects from SF_5CF_2I and $SF_5CF_2CF_2Br$ with piperidine in pentane.*

Table 2-9. *Halogen bonding effect from $SF_5CF_2CF_2Br$ and 2-methylpyrazine in pentane*

	Base (equiv.)	FS- (ppm)	Δ1	F_4S- (ppm)	Δ2	SF_5CF_2- (ppm)	Δ3	$SF_5CF_2CF_2$- (ppm)	Δ4
1	0	64.6006	0.0000	46.2264	0.0000	-91.5224	0.0000	-65.4264	0.0000
				46.7497	0.0000				
2	0.5	64.6122	0.0116	46.2264	0.0000	-91.5224	0.0000	-65.4264	0.0000
				46.7497	0.0000				
3	5.5	64.6123	0.0117	46.2264	0.0000	-91.5224	0.0000	-65.4496	-0.0232
				46.7497	0.0000				
4	11.7	64.6123	0.0117	46.2264	0.0000	-91.5224	0.0000	-65.4496	-0.0232
				46.7497	0.0000				
5	26.6	64.6355	0.0349	46.2380	0.0116	-91.5108	0.0116	-65.4728	-0.0464
				46.7613	0.0116				

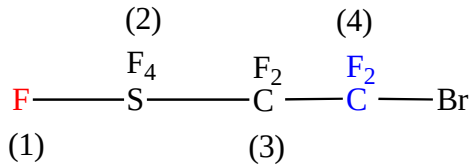


Table 2-10. *Halogen bonding effect from $SF_5CF_2CF_2Br$ and piperidine in pentane*

	Base (equiv.)	FS- (ppm)	Δ1	F_4S- (ppm)	Δ2	SF_5CF_2- (ppm)	Δ3	$SF_5CF_2CF_2$- (ppm)	Δ4
1	0	64.5890	0.0000	46.2264	0.0000	-91.5224	0.0000	-65.4147	0.0000
				46.7497	0.0000				
2	1	64.6122	0.0232	46.2264	0.0000	-91.5224	0.0000	-65.4380	-0.0233
				46.7497	0.0000				
3	10	64.6239	0.0349	46.2264	0.0000	-91.5224	0.0000	-65.5310	-0.1163
				46.7497	0.0000				
4	30	64.6355	0.0465	46.2264	0.0000	-91.5108	0.0116	-65.6822	-0.2675
				46.7497	0.0000				

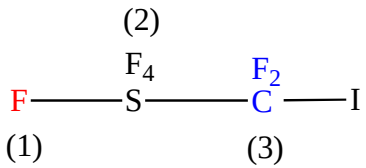


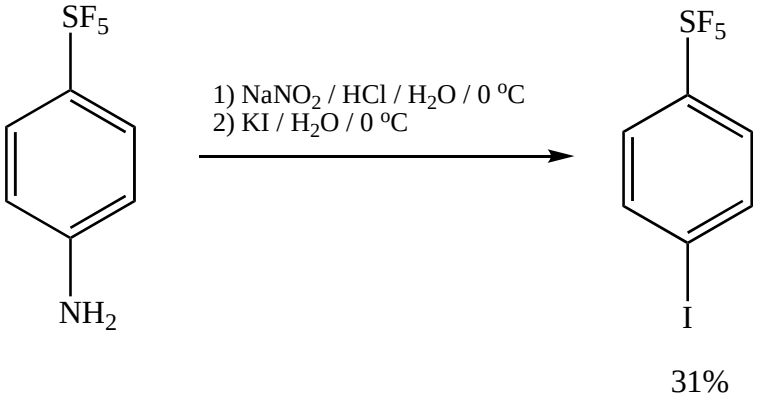
Table 2-11. *Halogen bonding effect from SF_5CF_2I and piperidine in pentane*

	Base (equiv.)	FS- (ppm)	Δ1	F_4S- (ppm)	Δ2	SF_5CF_2- (ppm)	Δ3
1	0	65.9031	0.0000	35.7717	0.0000	-24.8867	0.0000
				35.2483	0.0000		
2	1	67.1475	1.2444	36.0159	0.2442	-28.9918	-4.1051
				35.4926	0.2443		
3	9	69.1709	3.2678	36.4113	0.6396	-35.6786	-10.7919
				35.8880	0.6397		

2.2.9 Synthesis of 4-Iodo(pentafluorosulfanyl)benzene

Pentafluorosulfanyl-containing perfluoroalkylated halides were found to be unstable under the aforementioned reaction conditions used for studying halogen bonding. On the other hand, pentafluorosulfanyl-containing benzenes were reported to be stable under basic conditions.[15-16] Thus, 4-iodo(pentafluorosulfanyl)benzene ($SF_5C_6H_4I$) was selected as the synthetic target.

4-Iodo(pentafluorosulfanyl)benzene was prepared from (4-aminophenyl)-sulfur-pentafluoride by the synthetic route reported by Philp *et al*. (**Scheme 2-32**).[16] However, the yield of 4-iodo(pentafluorosulfanyl)benzene was very low due to the high volatility of $SF_5C_6H_4I$ (31%).



Scheme 2-32. *Synthesis of 4-iodo(pentafluorosulfanyl)benzene.*

2.3 Summary

In conclusion, an easily scalable route for the synthesis of pentafluorosulfanyldifluoroacetic acid **4** was developed. The rebirth of this more stable and

easily handled pentafluorosulfanyl-containing building block should encourage the further development and application of the SF_5 group into organic molecules. Meanwhile, it was discovered that the bulky SF_5 group can be a good leaving group under certain reaction conditions. More methodological studies are required in order to fully understand the special characteristics of the SF_5 group if one is to prevent this unwanted release. Furthermore, the first SF_5-containing fullerene, namely 1,7-$(SF_5CF_2CF_2)_2$-C_{60}, was prepared *via* a radical addition pathway. The preparation of 1,7-$(SF_5CF_2CF_2)_2$-C_{60} should further enhance the applications of SF_5 chemistry, especially in the area of materials chemistry. On the other hand, improved synthetic strategies leading to better atom economical efficiency are still needed in order to reduce the amount of $SF_5CF_2CF_2I$ being applied. With respect to halogen bonding of pentafluorosulfanyl-containing perfluoroalkylated halides, neither SF_5CF_2I or $SF_5CF_2CF_2Br$ were found to be stable with Lewis bases in THF, but the halogen bonding effect was detected by ^{19}F NMR spectroscopy when SF_5CF_2I or $SF_5CF_2CF_2Br$ was mixed with Lewis bases in pentane.

2.4 Experimental Section

2.4.1 General Experimental Methods

2.4.1.1 Glass and Metal Vacuum System

A borosilicate vacuum line equipped with Kontes Teflon® stopcocks was used for compounds that are normally moisture sensitive, volatile, and/or gases. Corrosive

compounds and high pressure processes are handled on a metal vacuum line. The vacuum system contains an upper manifold, a lower manifold with built in trap to trap separation system, a liquid nitrogen tap, and a mechanical vacuum pump as shown in **Figure 2-16**. A Monel pressure gage was used to measure the pressure of gases and volatile samples being transferred within the system. A Teledyne Hastings-Raydist Model DV-6M was used to measure the vacuum level in microns. An ultimate vacuum of 10^{-4} Torr could be achieved on the system.[91]

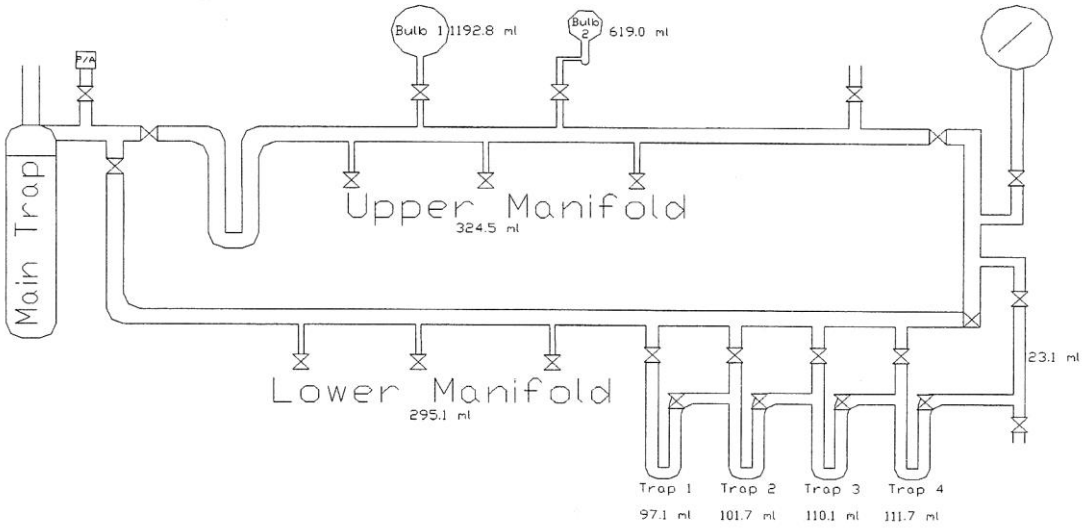


Figure 2-17. *Vacuum line system.*[91]

2.4.1.2 Instrumentation

NMR spectroscopic studies were processed at ambient temperature with an JOEL ECX 300 NMR instrument and a Bruker Avance 300 NMR instrument. The frequencies and solvents used are described separately for each substance. NMR spectra were measured

using solutions of 1-2 mmol/L concentrations in an appropriate deuterated solvent. All chemical shifts are given in units of the δ scale in ppm. Chemical shifts for ^{1}H NMR spectra are given respective to the proton signal of the solvent being used (acetonitrile 1.94 ppm, chloroform 7.25 ppm, dimethyl sulfoxide 2.50 ppm, methanol 3.35 ppm, toluene 7.00 ppm, water 4.75 ppm), while for ^{13}C NMR spectra the chemical shifts are respective to the deuterated solvent (acetonitrile 118.69 ppm, chloroform 77.0 ppm, dimethyl sulfoxide 37.7 ppm, methanol 49.3 ppm). ^{19}F NMR chemical shifts are referenced to either $CFCl_3$ (0.0 ppm) or trifluorotoluene (-63.72 ppm). Dry NMR solvents are prepared using an appropriate drying agent followed by storage over molecular sieves. Dry solvents are degassed and stored in glass bulbs fitted with glass-PTFE valves. Air sensitive NMR samples are prepared in 5 mm o.d. J. Young NMR tubes, whereby the samples and dry solvents can then be vacuum transferred into the NMR tube. Negative chemical shifts indicate upfield signals with respect to 0.00 ppm, while positive chemical shifts indicate downfield signals. The multiplicities of the signals are abbreviated by the following letters: s (singlet), d (doublet), dd (doublet of doublets), dm (doublet of multiplets), td (triplet of doublets), tt (triplet of triplets), q (quartet), quin (quintet), m (multiplet), bs (broad singlet), and n (asymmetric nonet), while coupling constants are given in Hertz (Hz).

GC/MS data were collected on a SHIMADZU GCMS-QP5000 mass spectrometer, while ATR-IR spectra were collected on a Thermo Scientific Nicolet iS5 diamond ATR spectrometer. A Branson 2510 ultrasonic bath was used to dissolve fullerene.

2.4.2 Materials

All solvents were dried over 3 Å molecular sieves prior to use. Copper powder (Aldrich, 99%, 45 μm), fullerene-C_{60}/C_{70} (75/25), and fullerene-C_{60} (99.5%) were used as received. Air sensitive chemicals were handled with a vacuum line and stored either in a glove box filled argon gas or in sealed flask with a PTFE valve. The compounds TFE/CO_2, S_2F_{10}, $ClFC=CF_2$ were available from laboratory stock. Carbon dioxide was scrubbed from the TFE/CO_2 mixture prior to use by passing the mixture through an aqueous caustic solution (20 wt% KOH).

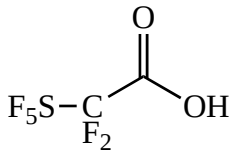
2.4.3 Synthesis of 1-Pentafluorosulfanyl-2-bromochlorotrifluoroethane

$SF_5CF_2CBrClF$ **10**

Chlorotrifluoroethylene (7.25 g, 62.3 mmol) and SF_5Br (9.05 g, 43.7 mmol) were condensed into 75-mL stainless steel Hoke® cylinder containing 0.2 g of 97% benzoyl peroxide (BPO). The reaction mixture was slowly heated to 95 – 105 ºC and then shaken at this temperature for 12 h. Thereafter, the reaction mixture was cooled to room temperature and any excess of SF_5Br was removed. The reaction mixture was washed with 10% aqueous $NaHCO_3$, water, and then dried over P_2O_5. An amount of 12.5 g (89%) of compound **10** with 96 – 97% purity (based on ^{19}F NMR spectrum) was obtained. Further distillations usually help to increase the purity of the product but sharply reduce the yield due to its high volatility. Thus, after two distillations only 7.2 g of compound **10** was

collected as the main fraction in nearly 99% purity. The spectroscopically pure product was obtained only after multiple fractional distillations. Since the aforementioned impurities do not affect the following steps, it is sufficient to perform only one distillation of the crude compound **10**. $SF_5CF_2CBrClF$: **^{19}F NMR** (283 MHz, CD_3CN) δ 65.1 (quin, *J* = 144 Hz, 1 F), 47.9 (dm, *J* = 144 Hz, 4 F), -76.7 (bs, 1 F), -84.3 and -86.9 (AB spin system, J_{AB} = 195 Hz, 2 F). **^{13}C NMR** (75.5 MHz, CD_3CN) δ 122.7 (tm, *J* = 313 Hz), 101.06 (dt, *J* = 313, 33 Hz). **HRMS (EI)** mass calculated for (C_2BrClF_8S) Cald.: 321.8465, found: 321.8460.

2.4.4 Synthesis of Pentafluorosulfanyldifluoroacetic Acid



4

Compound **10** (7.33 g, 22.7 mmol) and 60% oleum were placed into a 150-mL, heavy-walled Schlenk bomb, and the reaction mixture was stirred at room temperature for 2 days. Oleum with a higher concentration of SO_3 (up to 65 – 70%) may be used as well. The product was isolated by trap-to-trap distillation through two traps cooled to -90 and -196 °C, respectively. The gaseous product, pentafluorosulfanyldifluoroacetyl fluoride [$SF_5CF_2C(O)F$] was collected in the first trap. The crude material was purified with Hg to remove any bromine and chlorine derivatives, giving 4.67 g (92%) of a colorless gas.

Pentafluorosulfanyldifluoroacetyl fluoride without further purification was hydrolyzed in the following way. An amount of 2.24 g (10 mmol) of $SF_5CF_2C(O)F$ was

condensed into heavy-walled Schlenk flask equipped with a stirring bar and containing 0.24 g of DI water and small amount of silica gel (ca. 0.5 g). After warming to room temperature, the reaction mixture was stirred for 2 days. Then 4.8 mL of concentrated sulfuric acid was slowly added to the reaction mixture, and the flask was sealed and stirred at 100 °C for 24 h. Vacuum distillation of the reaction mixture produced 1.82 g, 82% of pentafluorosulfanyldifluoroacetic acid **4**. **^{1}H** NMR (300 MHz, $CDCl_3$) δ 11.09 (s, 1 H). **^{19}F NMR** (283 MHz, $CDCl_3$) δ 64.2 (quin, *J* = 147 Hz, 1 F), 41.7 (dm, *J* = 147 Hz, 4 F), -92.3 (qn, *J* = 11 Hz, 2 F). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 162.64 (t, *J* = 29 Hz), 117.83 (tqn, *J* = 308, 29 Hz). **HRMS (EI) mass** calculated for (CF_7S) calcd.: 176.9609, found: 176.9606.

2.4.5 Synthesis of Pentafluorosulfanyldifluoroiodomethane

SF_5CF_2I, **5**

An amount of 3.90 g (17.5 mmol) compound **4** was condensed into a 20-mL flask containing 5.05 g (21.8 mmol) Ag_2O in 10 mL of ether. The reaction mixture was stirred at room temperature for 2 days. The reaction mixture was then washed with ether and filtered 3 times, with the filtrate being collected in a round-bottomed flask. The ether was removed via rotary evaporation in a dark room. The flask was then connected to a vacuum line to remove any remainging solvent while being held at room temperature for 24 h. Therefore, the flask was moved into a desiccator containing P_2O_5 and held under vaccum for another 2 days. An amount of 5.51 g (16.44 mmol) of dry $SF_5CF_2C(O)OAg$ was collected, with yield for this step being 94%. Next, a mixture of 5.41 g (16.42 mmol)

$SF_5CF_2C(O)OAg$ and 19.83 g (78.13 mmol) anhydrous I_2 were heated to 200 °C. The crude SF_5CF_2I was collected by trapping the volatile components at liquid nitrogen temperature. The crude product was further purified by placement over Hg in order to remove the remaining I_2, and thereafter 0.98 g (1.65 mmol) of SF_5CF_2I was isolated via vacuum transfer. The yield for this step is only 20%. **^{19}F NMR** (283 MHz, $CDCl_3$) δ 65.1 (quin, J = 148 Hz, 1 F), 35.5 (dm, J = 148 Hz, 4 F), -24.3 (m, 2 F). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 93.9 (tquin, $^1J_{C\text{-}F}$ = 359 Hz, $^3J_{C\text{-}F}$ = 32 Hz, 1 C).

2.4.6 Synthesis of Pentafluorosulfanyltetrafluoroethyl Bromide

$SF_5CF_2CF_2Br$ **6**

An amount of 6.52 g (31.5 mmol) SF_5Br and 3.01 g (30.1 mmol) TFE were condensed into a 75-mL stainless steel Hoke® cylinder containing 0.17 g of 97% benzoyl peroxide (BPO). The reaction mixture was slowly heated to 80 – 90 ºC and then shaken at this temperature for 12 h. Thereafter, the reaction mixture was cooled to room temperature, and any excess of SF_5Br was removed. The product mixture was then washed with 10% aqueous $NaHCO_3$, water, and then dried over P_2O_5. An amount of 7.29 g (73%) of compound **6** with 96 – 97 % purity (based on ^{19}F NMR spectrum) was obtained. **^{19}F NMR** (283 MHz, $CDCl_3$) δ 64.2 (quin, J = 148 Hz, 1 F), 46.7 (dm, J = 148 Hz, 4 F), -91.5 (tm, J = 13 Hz, 2 F), -64.7 (tm. J = 10 Hz, 2 F). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 114.1 (tt, $^1J_{C\text{-}F}$ = 316 Hz, $^3J_{C\text{-}F}$ = 37 Hz 2F, 1 C).

2.4.7 Synthesis of Pentafluorosulfanyltetrafluoroethyl Iodide

$SF_5CF_2CF_2I$ **7**

To a 150-mL stainless steel cylinder equipped with a stainless-steel valve, 10.06 g (28.51 mmol) of ICF_2CF_2I was added at 0 °C. The reaction vessel containing ICF_2CF_2I was cooled to -196 °C and evacuated, and then 2.57 g (25.70 mmol) of $CF_2=CF_2$ and 6.90 g (27.15 mmol) of S_2F_{10} were added successively. The reaction vessel was wrapped with heating tape and heated at 165 °C for 13.0 h with continuous shaking. The reaction was quenched with cold water and then frozen at -20 °C overnight. The cylinder was then slowly warmed to the room temperature, and the excess pressure was released to a 20 wt% aqueous KOH solution. The product mixture was collected as a violet liquid by vacuum transfer. Finally, an amount of 7.43 g (21.0 mmol) of $SF_5CF_2CF_2I$ (40.8% yield based on $CF_2=CF_2$ applied, 98% purity determined by NMR) was collected at 64 °C by fractional distillation of the crude product followed by treatment with Hg (0.40 mL × 2) to remove any remaining iodine. **^{19}F NMR** (300 K, toluene-D8, 282 MHz): δ 64.0 (quin, 1F, $^2J_{F,F}$ = 147 Hz), 46.2 (d, 4F, $^2J_{F,F}$ = 147 Hz), -65.4 (m, 2F, $^3J_{F,F}$ = 11 Hz), -91.7 (t, 2F, $^3J_{F,F}$ = 14 Hz).**^{13}C NMR** (300K, $CDCl_3$, 75 MHz): δ 119.2 (tm, 2C, $^1J_{C,F}$ = 306 Hz), 91.3 (tt, 2 C, $^1J_{C,F}$ = 323, $^2J_{C,F}$ = 41 Hz).**MS (EI)** *m/e* 354 [M^+], 227 (24%) [M-I^+], 208 (4%) [M-I-F^+], 177 (26%) [M-I-CF_2^+], 158 [SF_5CF^+], 127 (38%) [SF_5^+, I^+], 119 (100%) [$C_2F_5^+$], 100 (58%) [$C_2F_4^+$].

2.4.8 Synthesis of 1,7-$(SF_5CF_2CF_2)_2$-C_{60}

1,7-$(SF_5CF_2CF_2)_2$-C_{60} **8**

Fullerene C_{60} powder (18.7 mg, 0.026 mmol) was mixed with *o*-DCB (3 mL) in a 10-mL Schlenk flask equipped with a PTFE-protected high vacuum valve and a magnetic stirring bar. The flask was placed in ultrasonic water bath for 1 h, and then the mixture was stirred overnight to form a homogeneous solution. To the liquid obtained, 4 equiv. of $SF_5CF_2CF_2I$ (16.6 μL, 0.104 mmol) was added via a micro syringe, then 1.85 g copper powder was carefully transferred into the flask, and the mixture was diluted with another 3 mL of *o*-DCB. The Schlenk flask was connected to a vacuum line to remove air, and then the reaction vessel was placed in oil bath that had been preheated to 145 °C. The color of solution changed from violet to deep brown during the period of heating. After 72 h, the reaction flask was cooled with cold water and then stored in a refrigerator overnight. The reaction mixture was then filtered, and the resulting solid residue was washed with *o*-DCB. A deep brown colored crude compound **8** was collected after removing the solvent via high vacuum at 55 °C. *A ^{19}F NMR spectrum study of a sample of the crude product containing $C_6H_5CF_3$ as an internal standard indicated that 16% of $SF_5CF_2CF_2I$ was unreacted and remained in the crude reaction mixture and 1.14 equiv. of $SF_5CF_2CF_2$- had added to fullerene based on the amount of C_{60} used.* **^{19}F NMR** (crude product, 300 K, toluene-D8, 282.40 MHz): δ 66 (bs, 1F,), 45 (dm, 4F), -88 (bs, 2F), -107 to -111 (m, 2F). **MS (ESI)** *m/e* 1174 [M^-].

Before heating

After heating

2.4.9 General Procedure for the Synthesis of Pentafluorosulfanyl-tetrafluoroethane

$SF_5CF_2CF_2H$ **9**

Method 1: The bromide $SF_5CF_2CF_2Br$ (0.41 g, 1.4 mmol) was added to tetraglyme (6 mL) in a 50-mL two-necked, round-bottomed flask under nitrogen gas protection. The mixture was then cooled to -196 °C and degassed. Tributyltin hydride (1.1 mL, 4.1 mmol) was slowly added over a 30-min period while the reaction mixture was held at -196 °C. The reaction mixture was then allowed to warm to room temperature slowly with stirring. After 12 h, the product (0.30 g, yield 96%) was collected by vacuum distillation.

Method 2: An amount of 2.5 mL of Et_3B solution (1M in hexane, 2.5 mmol) was slowly added to a flask containing $SF_5CF_2CF_2Br$ (0.76 g, 2.5 mmol) that had been

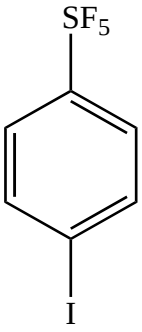
precooled to -30 °C. The reaction mixture was kept at this temperature for 2h with stirring. A ^{19}F NMR spectroscopic investigation of a sample of the reaction mixture indicated that 50% of $SF_5CF_2CF_2Br$ was converted to generate the $SF_5CF_2CF_2H$. However, it proved to be difficult to isolate $SF_5CF_2CF_2H$ from hexane.

^{19}F NMR (300 K, $CDCl_3$, 282 MHz): δ 65.1 (quin, 1F, $^2J_{F,F}$ = 146 Hz), 41.6 (dm, 4F, $^2J_{F,F}$ = 146 Hz), -101.3 (m, 2F), -135.2 (dm, 2F, $^2J_{F,H}$ = 52.0 Hz). **^{1}H NMR** (300 K, $CDCl_3$, 300 MHz): δ 6.1 (tt, 1H, $^2J_{H,F}$ = 51 Hz, $^3J_{H,F}$ = 6 Hz). **^{13}C NMR** (300 K, $CDCl_3$, 75 MHz): δ 107.8 (tt, 2C, $^1J_{C,F}$ = 257 Hz,), 121.3 (tm, 2C, $^1J_{C,F}$ = 323 Hz). **MS (EI)** *m/e* 127 (42%) [SF_5^+], 101 (100%) [M-SF_5^+], 177 (1%) [M-CF_2H^+], 89 (100%) [SF_3^+], 51 (100%) [CF_2H^+]. **IR** (KBr): 3018 (w), 1397 (m), 1361 (vw), 1267 (s), 1202 (s), 1149 (s), 1026 (m), 877 (vs), 809 (s), 685 (m), 608 (s), 585 (w), 562 (m), 418 (vw).

2.4.10 General Procedure for the Halogen Bonding Study in Solution Phase

A 1-mL PFA tube containing 0.4 mL pentane was cooled from 0 to -5 °C, and then the respective SF_5-containing perfluoroalkyl halide and a certain equivalent of Lewis base was slowly added with a micro syringe. The generated mixture was then stirred for 10 minutes. Thereafter, NMR samples were taken and ^{19}F NMR spectra were collected in 15 minutes.

2.4.11 Synthesis of 4-Iodo(pentafluorosulfanyl)benzene



A solution of cold (0 ºC) $NaNO_2$ (0.10 g, 1.4 mmol) in water (1 mL) was added slowly to a cold (0 ºC) solution of (4-aminophenyl)sulfurpentafluoride (0.22 g, 1.02 mmol) in a mixture of acetic acid and sulfuric acid (1:1). The reaction mixture was stirred at 0 ºC for 1 hour. Then a solution of sodium iodide (0.16 g, 1.07 mmol) in water was added slowly to the above reaction mixture. After work-up, 4-iodo(pentafluorosulfanyl)benzene was isolated as a white solid (0.10 g, 31%) by column chromatography. **^{19}F NMR** (283 MHz, $CDCl_3$) δ 83.6 (quin, 1F, *J* = 150 Hz), 62.8 (d, *J* = 150 Hz, 4 F). **^{1}H NMR** (300 K, $CDCl_3$, 300 MHz): δ 7.8 (d, 2H, $^{3}J_{H,H}$=9 Hz), δ 7.5 (d, 2H, $^{3}J_{H,H}$=9 Hz). **^{13}C NMR** (300K, $CDCl_3$, 75 MHz): δ 153.5 (quin, 2C, $^{2}J_{C,F}$ = 18 Hz,), 138.0 (s, 2C, *J* = 5 Hz), 127.6 (t, 2C). 98.3 (s)

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CHAPTER THREE

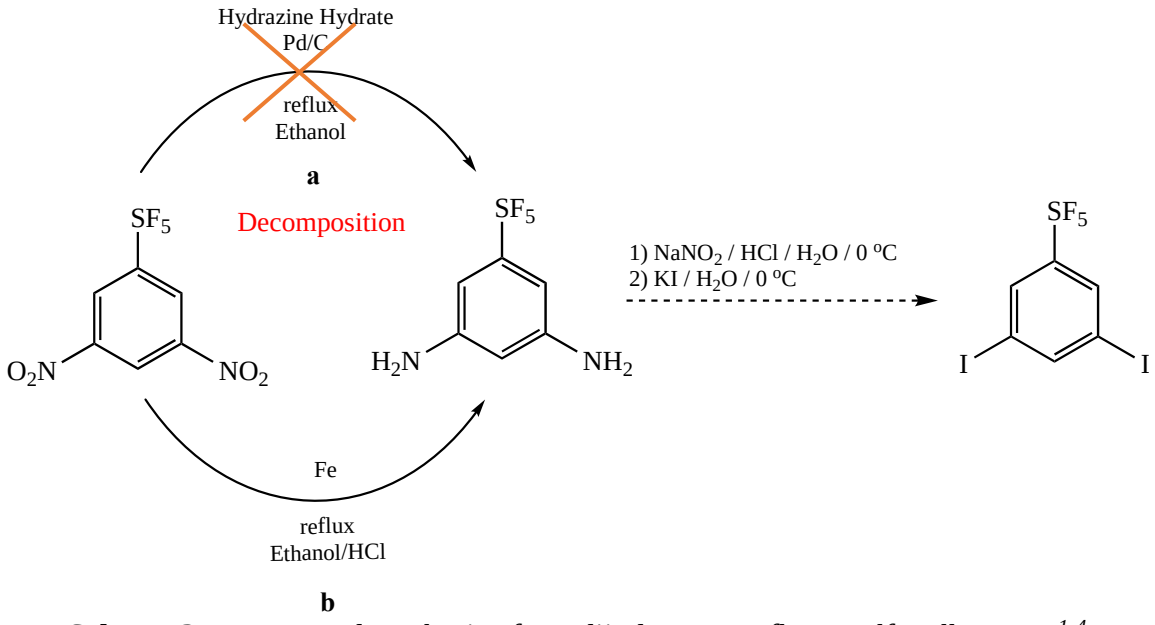
FUTURE DIRECTIONS

3.1 Halogen Bonding Effect of 1,3-Diiodo-5-pentafluoro-sulfanylbenzene

As the experimental results on the halogen bonding effect mentioned in **Section 2.2.8** indicate, pentafluorosulfanyl-containing perfluoroalkyl halides, such as SF_5CF_2I and $SF_5CF_2CF_2Br$ are not suitable Lewis acid because they are unstable in the presence of Lewis bases in THF. In addition, although the halogen bonding effect was observed for a mixture of SF_5CF_2I or $SF_5CF_2CF_2Br$ with Lewis bases in pentane, solid complexes were not formed on which additional proof of the halogen bonding effect could be found from a single crystal X-ray structure determination. It is anticipated that SF_5-containing aryl iodides would be good Lewis acid acceptors for the formation of halogen bonds with Lewis bases. Therefore, 1,3-diiodo-5-pentafluorosulfanylbenzene ($SF_5C_6H_3I_2$) was chosen as synthetic target for the investigation of halogen bonding.

The compound 1,3-dinitro-5-pentafluorosulfanylbenzene was used as a starting material for the preparation of 1,3-diiodo-5-pentafluorosulfanylbenzene. Initially, attempts to reduce 1,3-dinitro-5-pentafluorosulfanylbenzene with hydrazine hydrate and Pd/C in refluxing ethanol failed to give the precursor 1,3-diamino-5-pentafluorosulfanylbenzene (**Scheme 3-1**, Path a), and the pentafluorosulfanyl group was found to be partly

decomposed under these reaction conditions. Thrasher and co-workers reported that 1,2-diamino-4-pentafluorosulfanylbenzene and 1,4-diamino-2-pentafluorosulfanyl-benzene were formed from the reduction of the corresponding nitro-pentafluorosulfanylbenzenes with an excess amount of iron power in the presence of catalytic amounts of concentrated HCl in ethanol.[1-2] Meanwhile, Umemoto *et al*. disclosed in a patent the preparation of 1,3-diamino-5-pentafluoro-sulfanyl-benzene from 1,3-dinitro-5-pentafluorosulfanylbezene under the same acidic reaction condition.[3] Therefore, 1,3-diiodo-5-pentafluorosulfanylbenzene should be successfully obtained as shown the synthetic route of Path b in **Scheme 3-1**.[4] When 1,3-diiodo-5-pentafluorosulfanylbenzene is in hand, it will be possible to investigate the halogen bond effect of SF_5-containing aryl iodides.



Scheme 3-1. *Proposed synthesis of 1,3-diiodo-5-pentafluorosulfanylbenzene.*[1-4]

3.2 Synthesis of 1,7-$(SF_5CF_2CF_2)_2$-C_{60} under Mild Reaction Conditions

The thermal addition of $SF_5CF_2CF_2I$ to C_{60}/C_{70} gave 1,7-$(SF_5CF_2CF_2)_2$-C_{60}/C_{70} in low yield (**Section 2.2.7**). In addition, an excess amount of $SF_5CF_2CF_2I$ was required for this reaction and a lot of $SF_5CF_2CF_2I$ was decomposed into SF_4. Therefore, the preparation of 1,7-$(SF_5CF_2CF_2)_2$-C_{60}/C_{70} in high yield under mild reaction conditions is highly desirable.

Initially, triethylborane (Et_3B) was selected as the radical initiator for the addition of $SF_5CF_2CF_2I$ to C_{60}/C_{70}. A solution of C_{60}/C_{70} (18.7 mg) in solvent (2 mL) was cooled to -5 °C, then one to two equivalent of $SF_5CF_2CF_2I$ and Et_3B (1.0 M in hexane) was added to the solution. The reaction mixture was then slowly warmed to room temperature and stirred for 30 minutes at this temperature. (**Scheme 3-2**). The reaction conditions were screened as shown in **Table 3-1**, and the ^{19}F NMR spectrum of the reaction mixture was used to investigate the experimental results of this addition reaction (**Figure 3-1**).

$$C_{60}/C_{70} + SF_5CF_2CF_2I \xrightarrow[\text{-5 °C to r.t.}]{Et_3B} (SF_5CF_2CF_2)_2\text{-}C_{60}/C_{70}$$

Scheme 3-2. *Synthesis of 1,7-$(SF_5CF_2CF_2)_2$-C_{60} using Et_3B as radical initiator.*

Treatment of C_{60}/C_{70} with 0.3 equivalent of Et_3B and 1.0 equivalent of $SF_5CF_2CF_2I$ using *o*-DCB as solvent failed to give 1,7-$(SF_5CF_2CF_2)_2$-C_{60}/C_{70}(**Table 3-1**, entry 1 and **Figure 3-1**, 1). When the amount of Et_3B was increased to 1.0 equivalent using *o*-DCB as solvent (**Table 3-1**, entry 2), both 1,7-$(SF_5CF_2CF_2)_2$-C_{60}/C_{70} and $SF_5CF_2CF_2H$ were formed in very low yields (**Figure 3-1**, 2**)**. The formation of $SF_5CF_2CF_2H$ was further

proved when heptane was used as solvent (**Table 3-1**, entry 3 and **Figure 3-1**, 3), because heptane is also a good hydrogen atom donor. But the yield of 1,7-($SF_5CF_2CF_2$)$_2$-C_{60}/C_{70} was not improved using tetrachloroethane as solvent (**Table 3-1**, entry 4 and **Figure 3-1**, 4).

Table 3-1. *Reaction conditions for synthesis of 1,7-($SF_5CF_2CF_2$)$_2$-C_{60} using Et_3B as radical initiator*

entry	C_{60}/C_{70} (equiv.)	$SF_5CF_2CF_2I$ (equiv.)	Et_3B (equiv.)	Solvent
1	1.0	1.0	0.3	*o*-DCB
2	1.0	2.0	1.0	*o*-DCB
3	1.0	1.0	1.0	Heptane
4	1.0	1.0	1.0	Tetrachloroethane

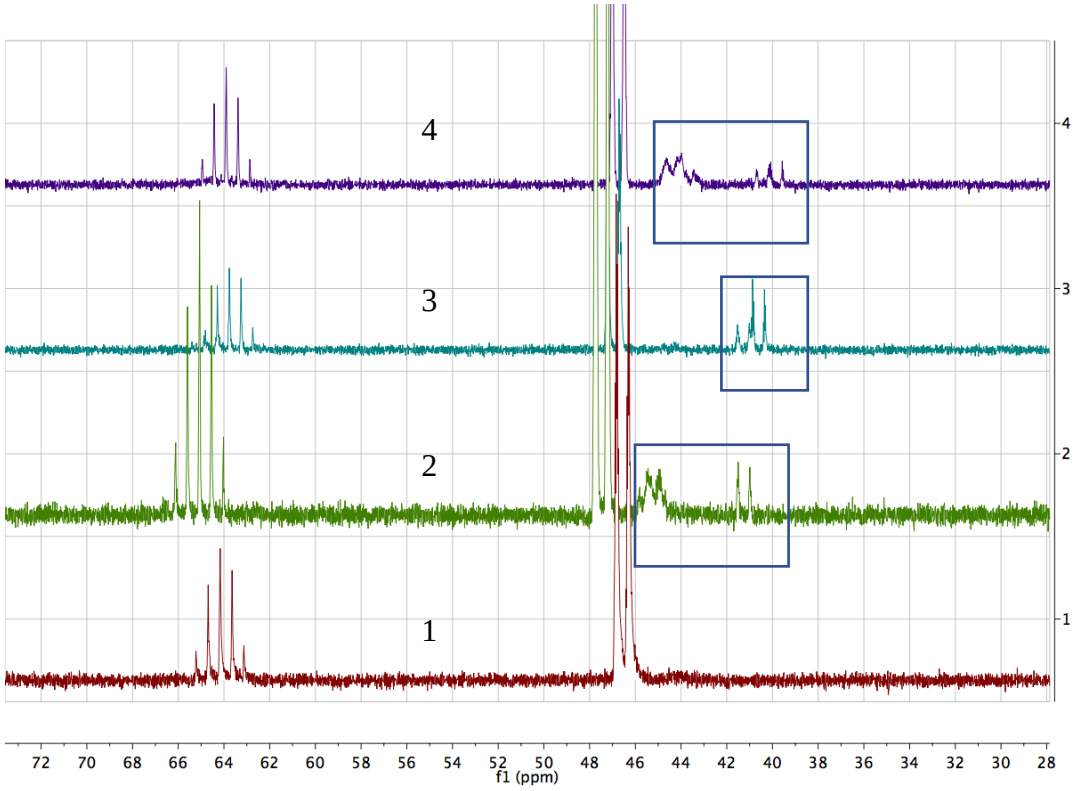


Figure 3-1. *^{19}F NMR spectra of the reaction mixture for the synthesis of 1,7-($SF_5CF_2CF_2$)$_2$-C_{60} using Et_3B as radical initiator under different reaction conditions.*

The formation of 1,7-$(SF_5CF_2CF_2)_2$-C_{60}/C_{70} using Et_3B as radical initiator under mild reaction condition was achieved, but the yield of the desired product is still too low. The use of a hydrocarbon solvent should be avoided to prevent the generation of a competitive by-product, $SF_5CF_2CF_2H$. Other radical initiators should be screened in order to improve the yield of 1,7-$(SF_5CF_2CF_2)_2$-C_{60}/C_{70}.

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APPENDIX

SELECTED NMR, IR, AND MASS SPECTRA OF FLUORINATED COMPOUNDS

The NMR, IR, and Mass spectra in this Appendix provide useful visual supplemental material for the characterization of some of the compounds prepared in Chapters One and Two.

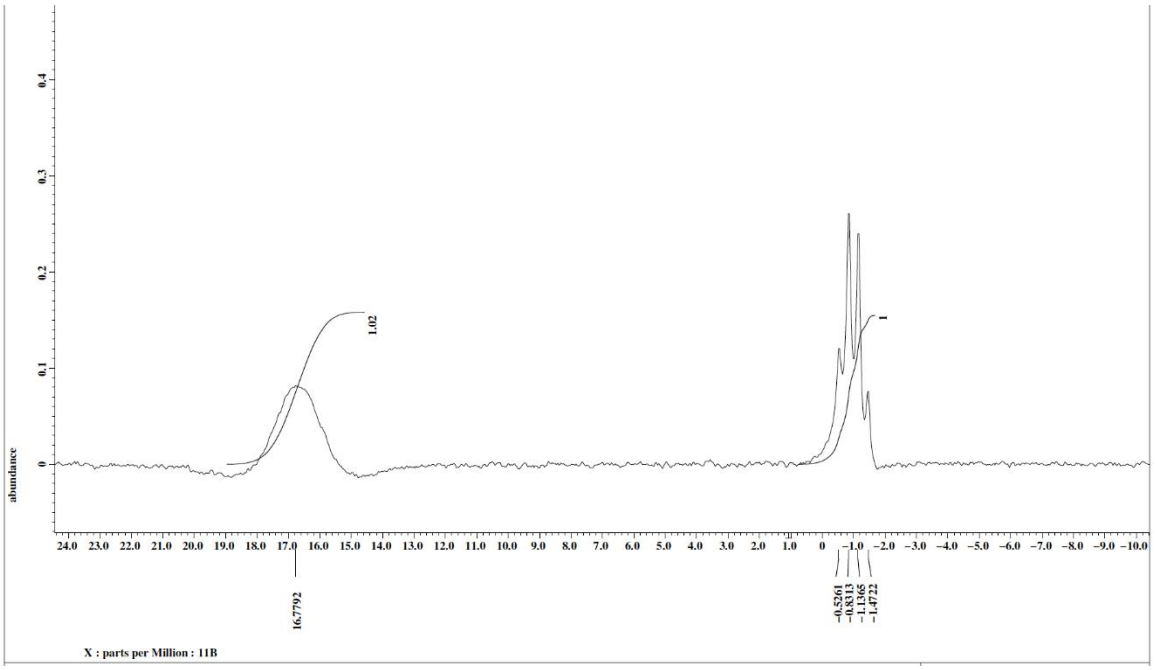

Figure A-1. *^{11}B NMR spectrum of the preparation of $K^+CF_3(BOMe)_3^-$.*

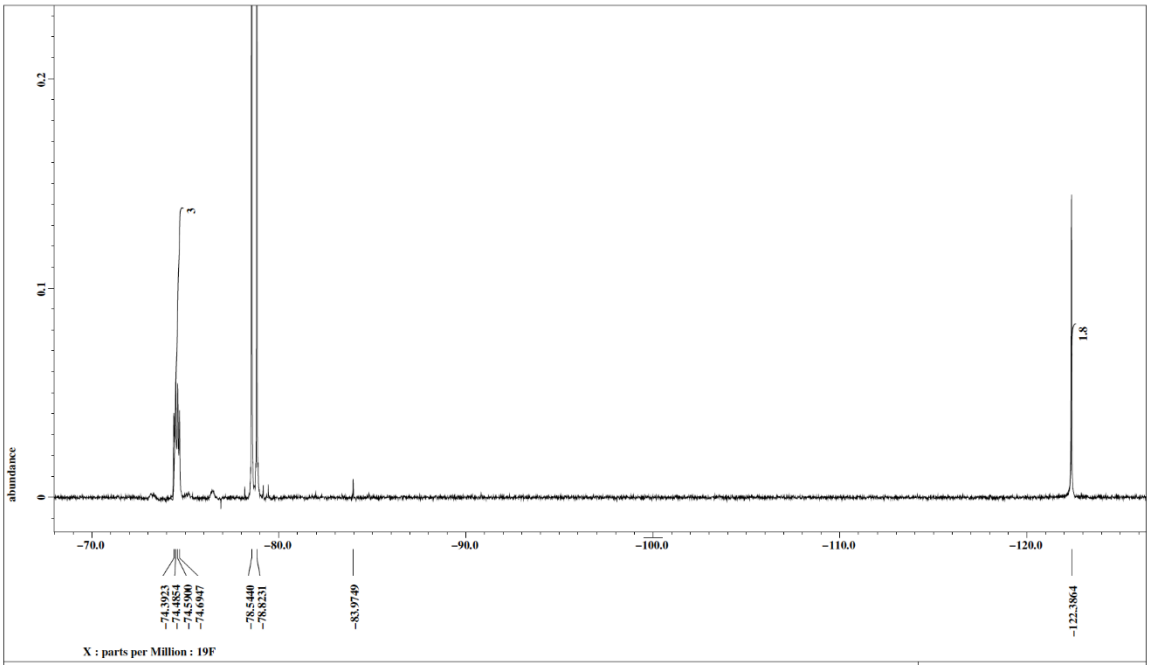

Figure A-2. *^{19}F NMR spectrum of the preparation of $K^+CF_3(BOMe)_3^-$.*

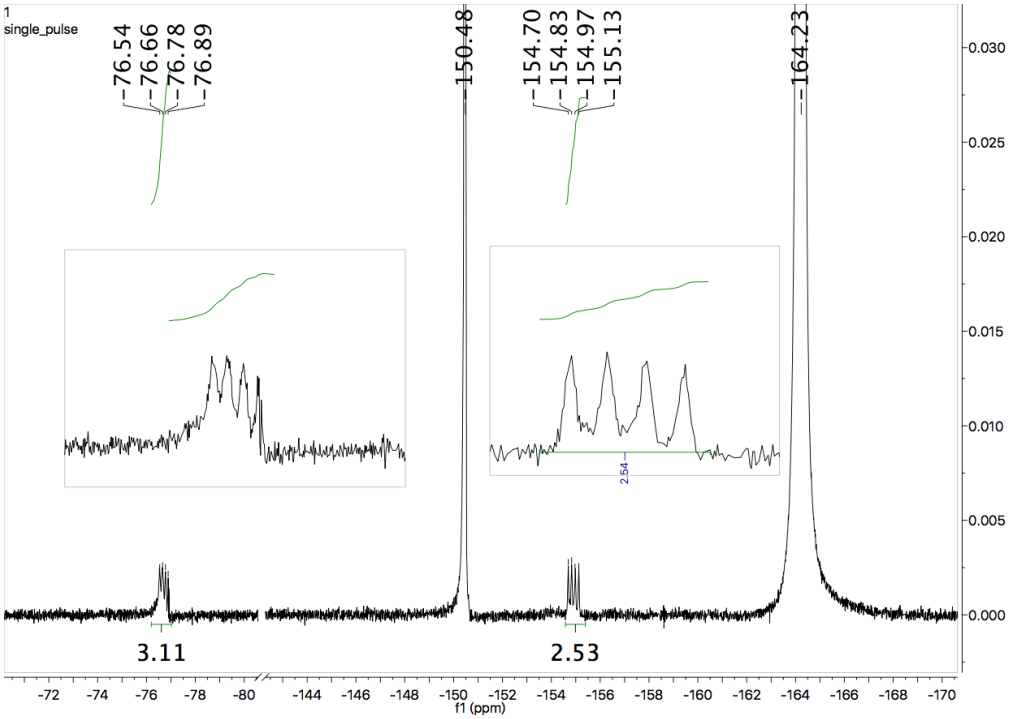

Figure A-3. *^{19}F NMR spectrum of the preparation of $K^{+}CF_3BF_3^{-}$.*

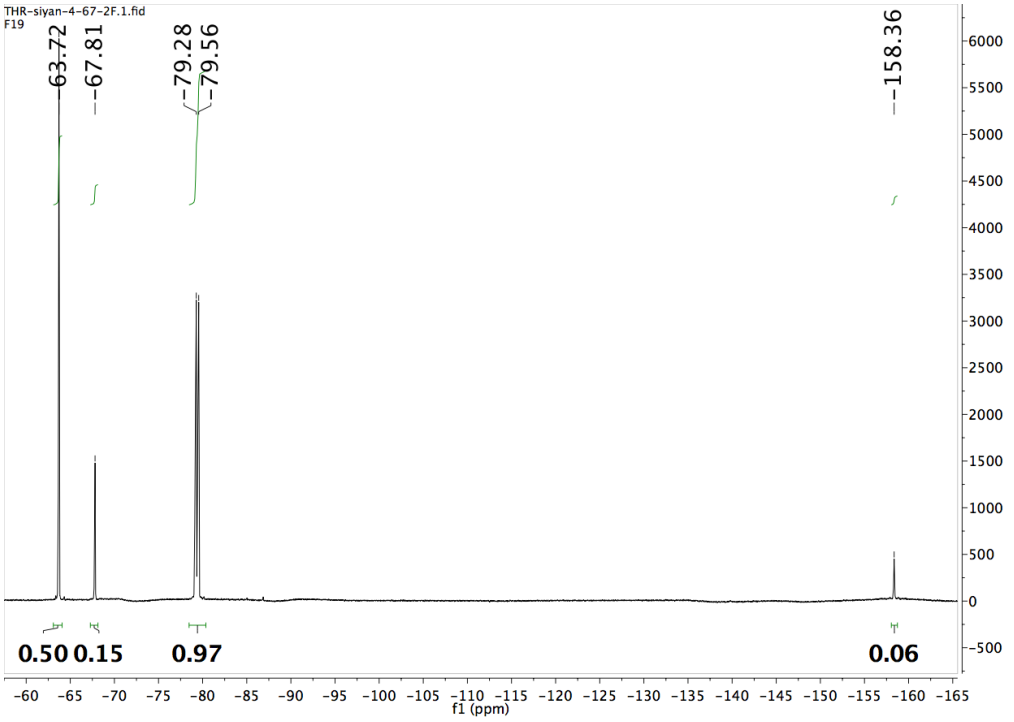

Figure A-4. *^{19}F NMR spectrum of the preparation of $TMSCF_3$.*

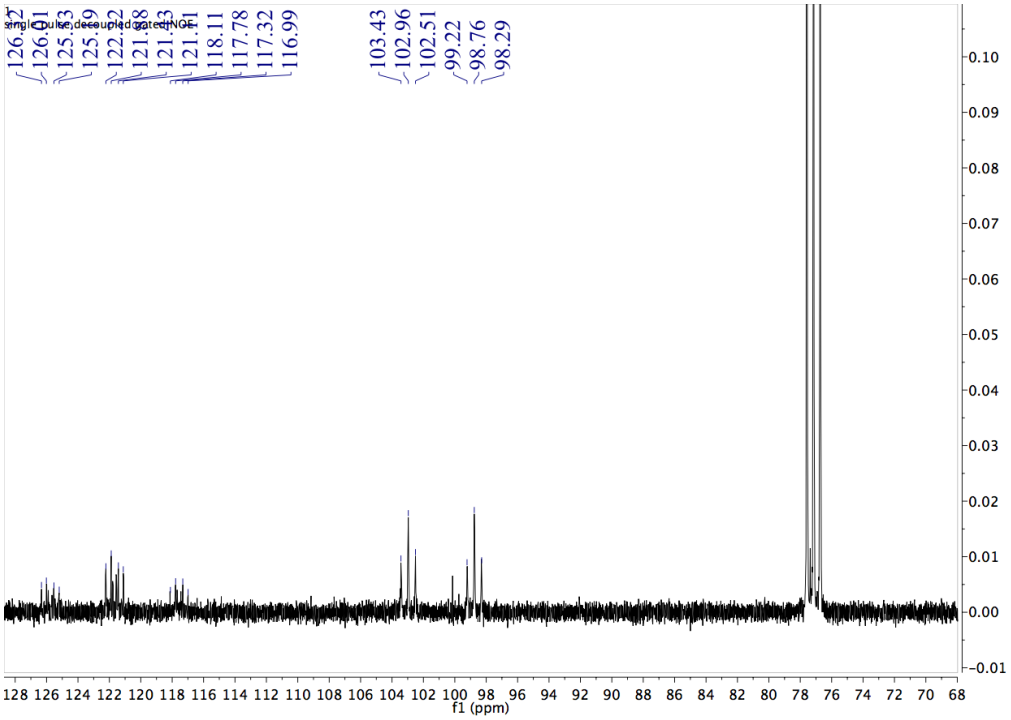

Figure A-5. *^{13}C NMR spectrum of $SF_5CF_2CFBrCl$.*

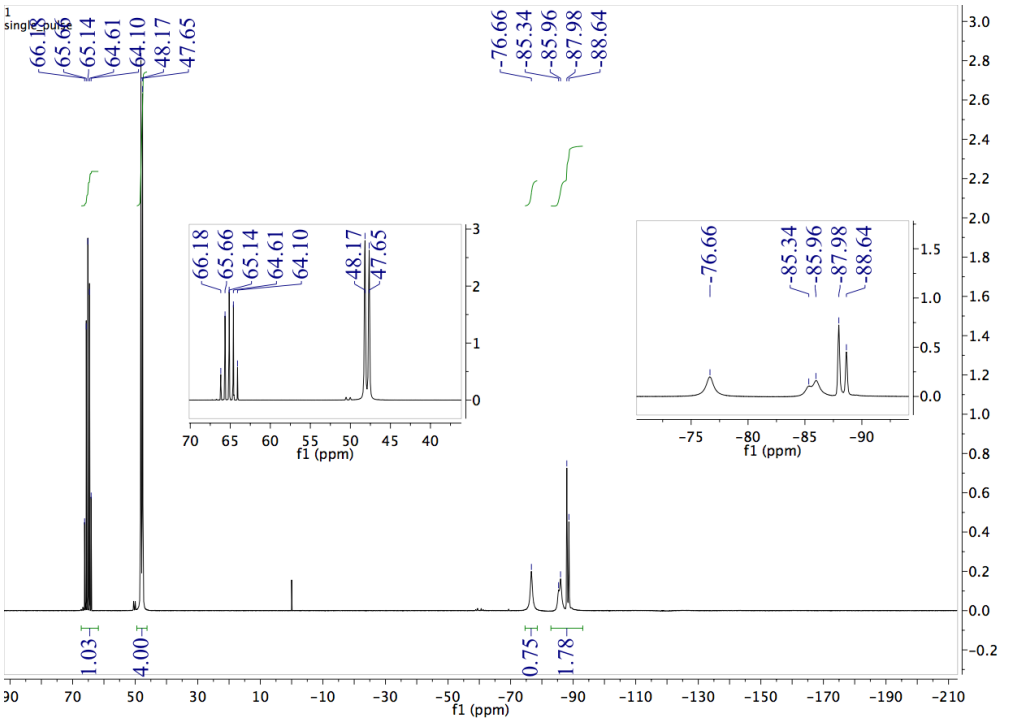

Figure A-6. *^{19}F NMR spectrum of $SF_5CF_2CFBrCl$.*

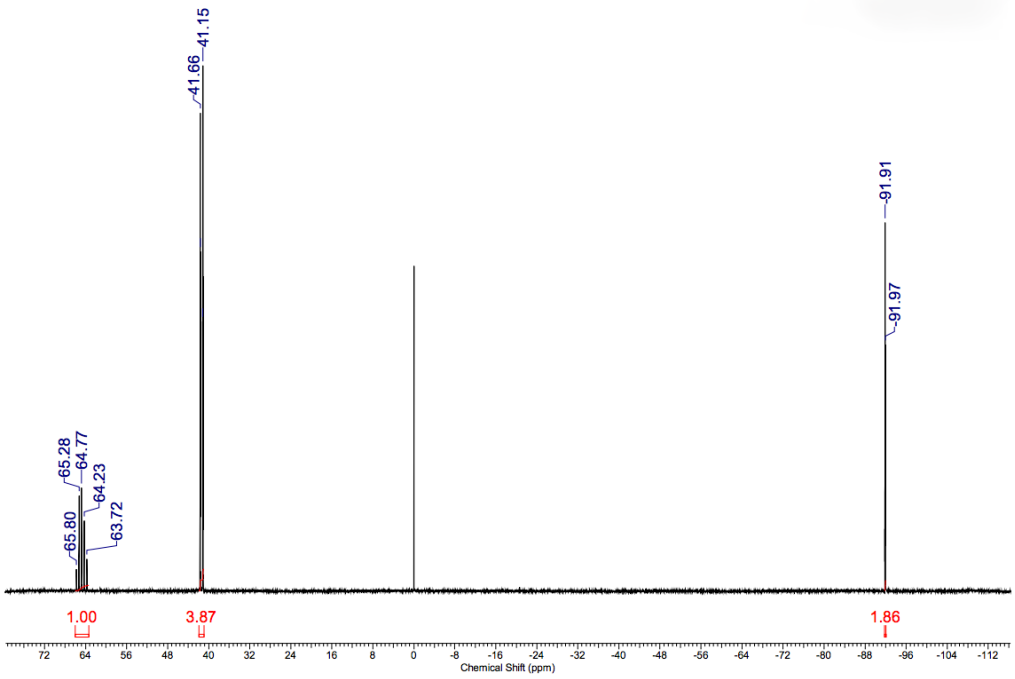

Figure A-7. *^{19}F NMR spectrum of $SF_5CF_2C(O)OH$.*

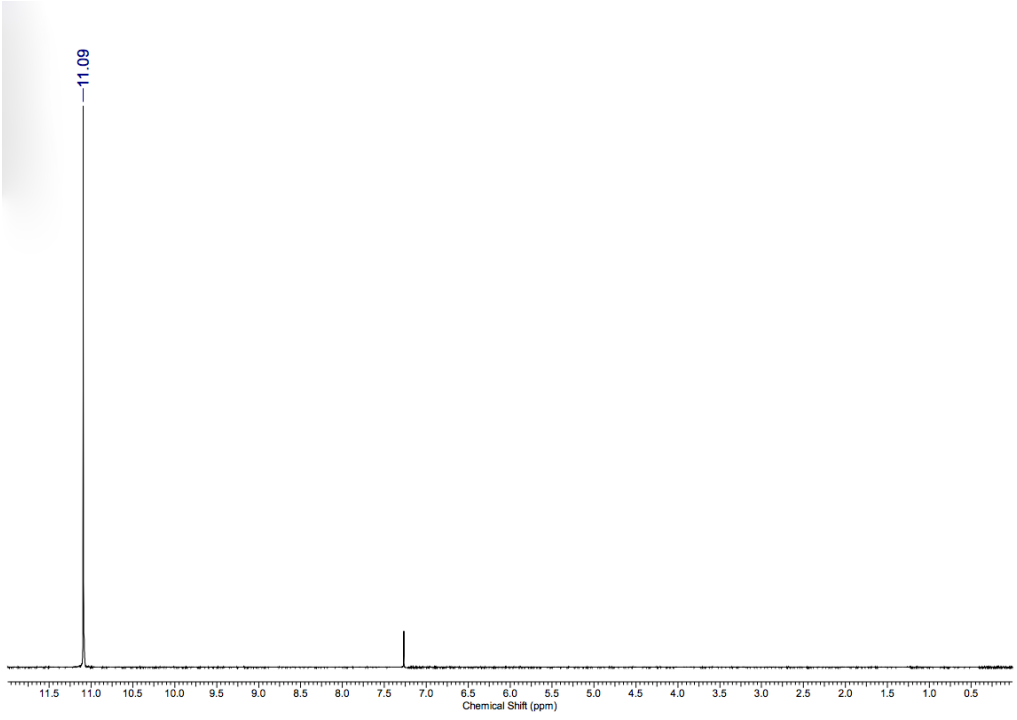

Figure A-8. *^{1}H NMR spectrum of $SF_5CF_2C(O)OH$.*

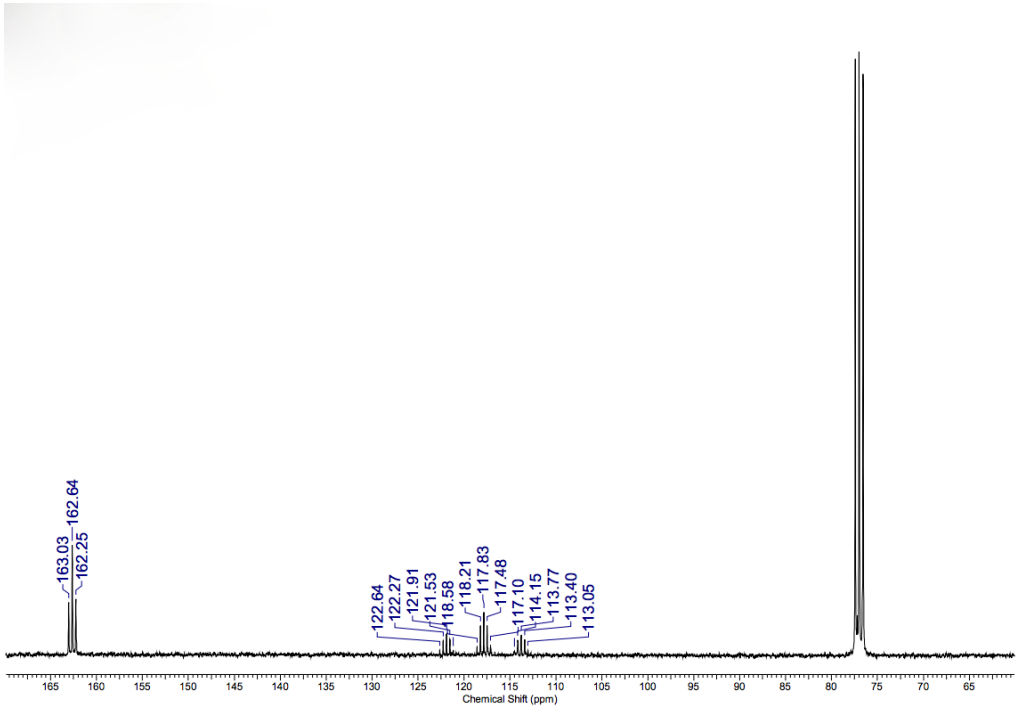

Figure A-9. *^{13}C NMR spectrum of $SF_5CF_2C(O)OH$.*

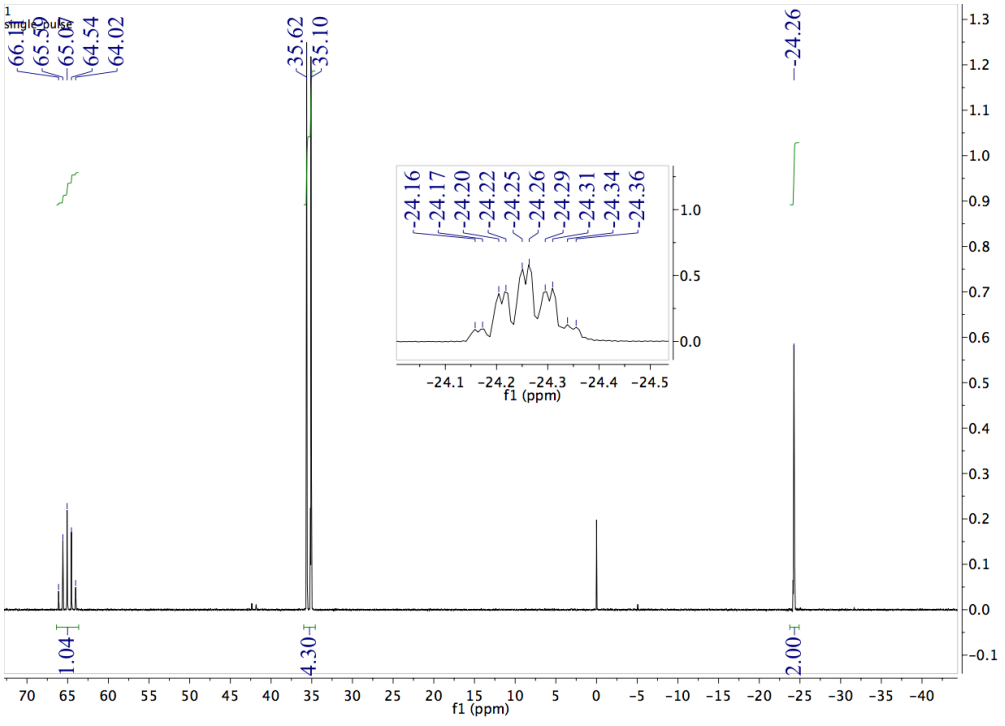

Figure A-10. *^{19}F NMR spectrum of SF_5CF_2I.*

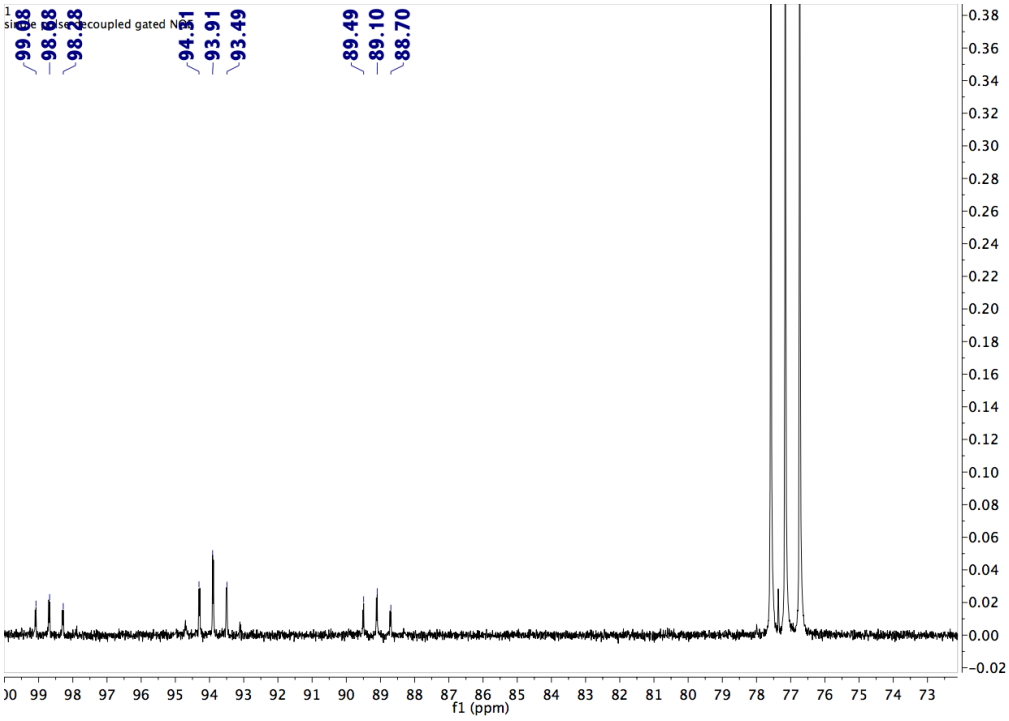

Figure A-11. *^{13}C NMR spectrum of SF_5CF_2I.*

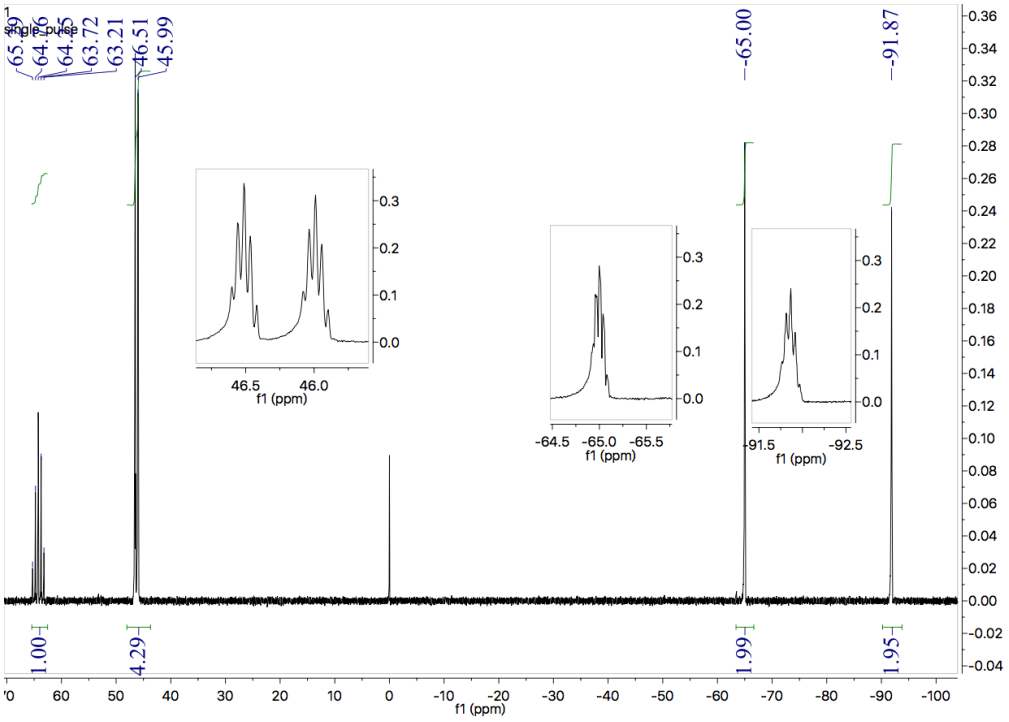

Figure A-12. *^{19}F NMR spectrum of $SF_5CF_2CF_2Br$.*

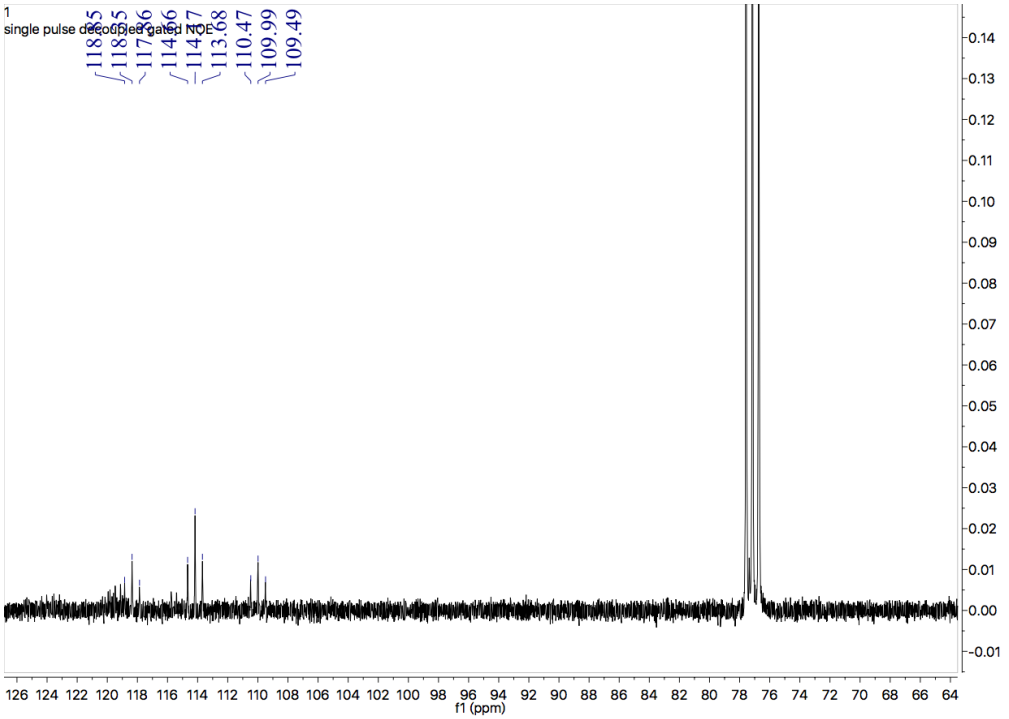

Figure A-13. *^{13}C NMR spectrum of $SF_5CF_2CF_2Br$.*

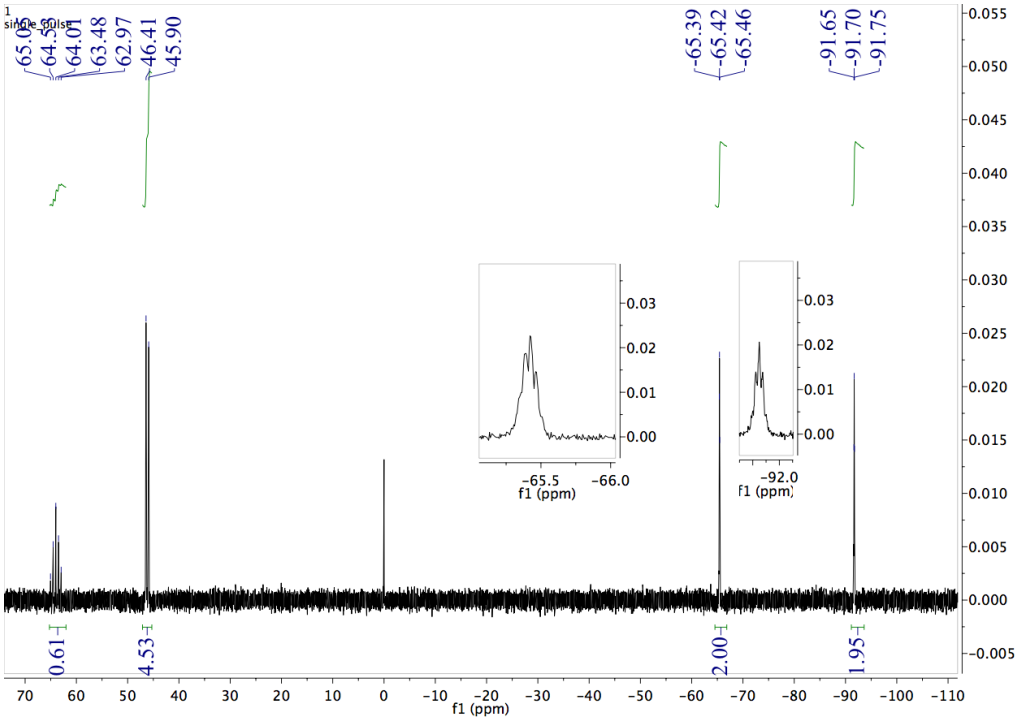

Figure A-14. *^{19}F NMR spectrum of $SF_5CF_2CF_2I$.*

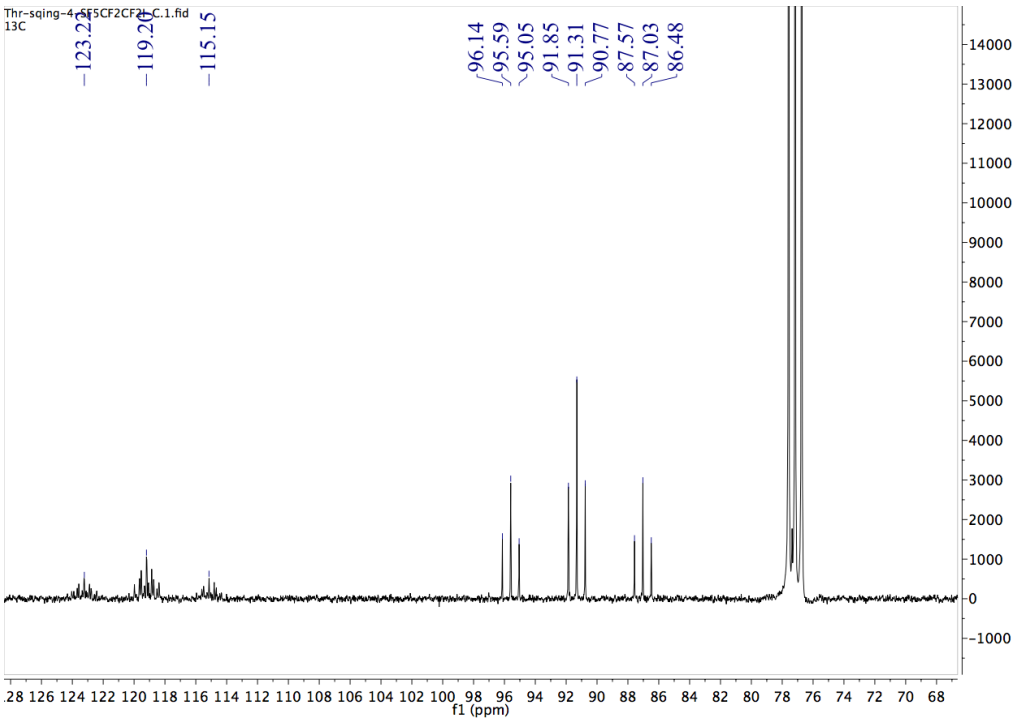

Figure A-15. *^{13}C NMR spectrum of $SF_5CF_2CF_2I$.*

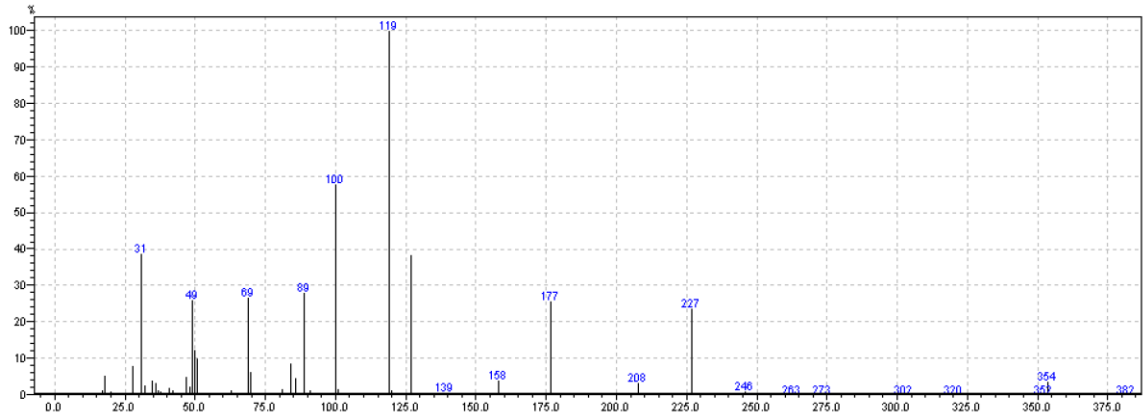

Figure A-16. *Mass spectrum of $SF_5CF_2CF_2I$.*

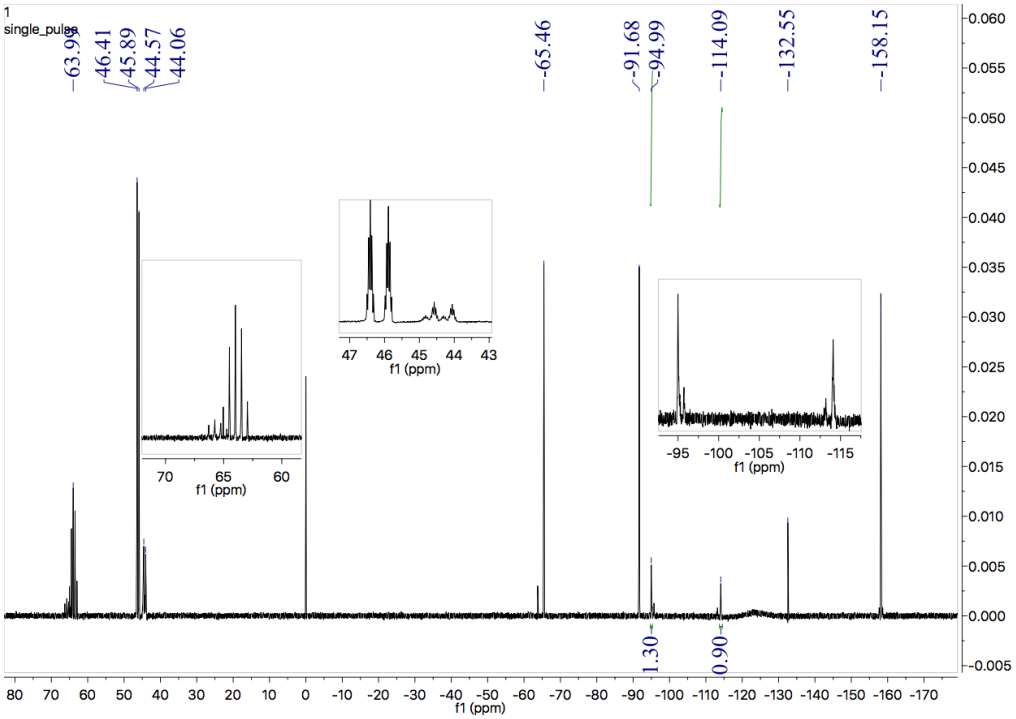

Figure A-17. *^{19}F NMR spectrum of the preparation of $TMSCF_2CF_2SF_5$.*

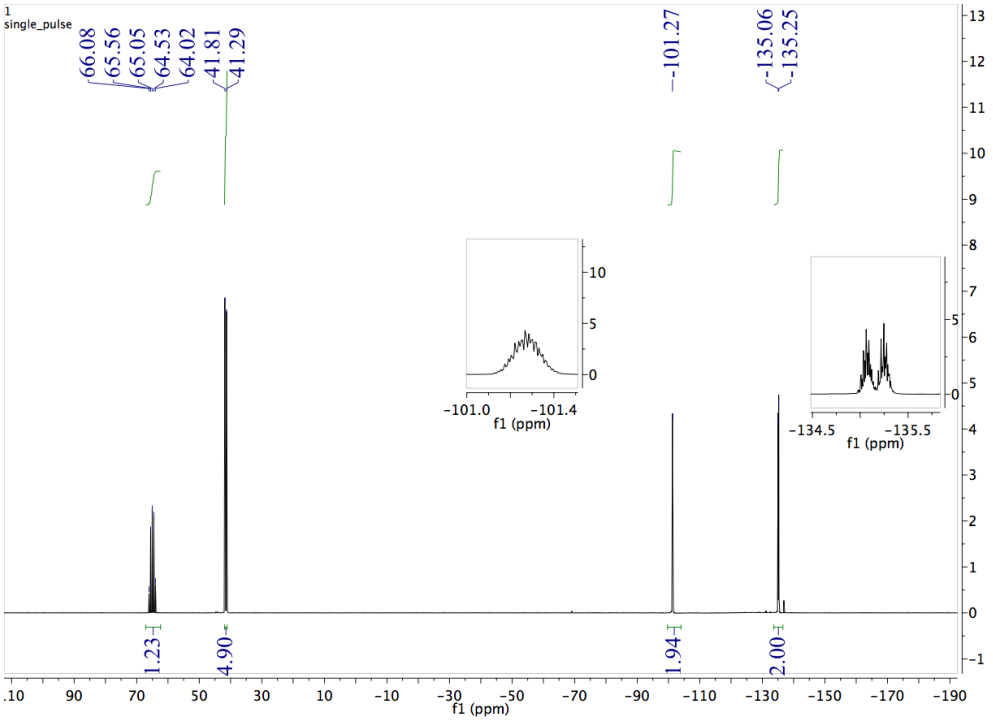

Figure A-18. *^{19}F NMR spectrum of the preparation of $SF_5CF_2CF_2H$.*

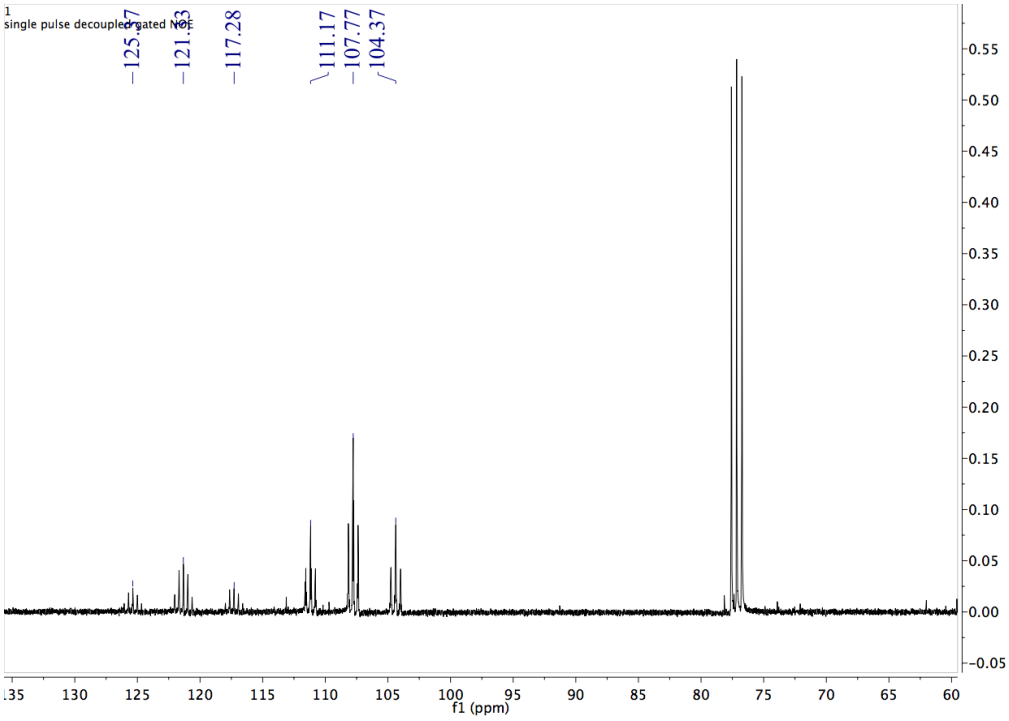

Figure A-19. *^{13}C NMR spectrum of the preparation of $SF_5CF_2CF_2H$.*

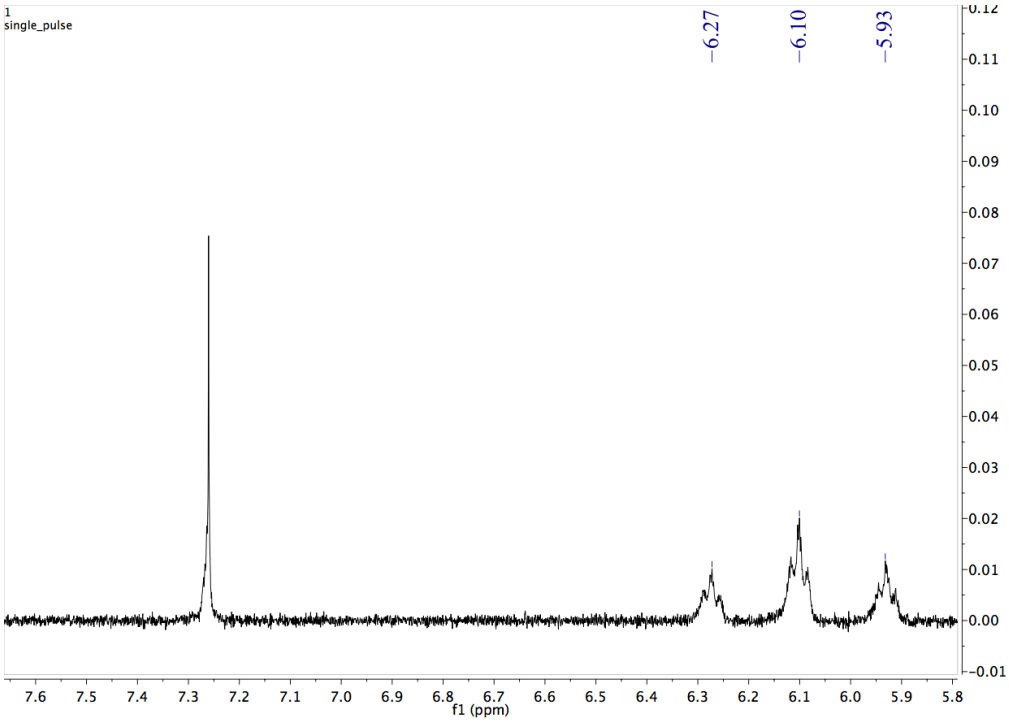

Figure A-20. *^{1}H NMR spectrum of the preparation of $SF_5CF_2CF_2H$.*

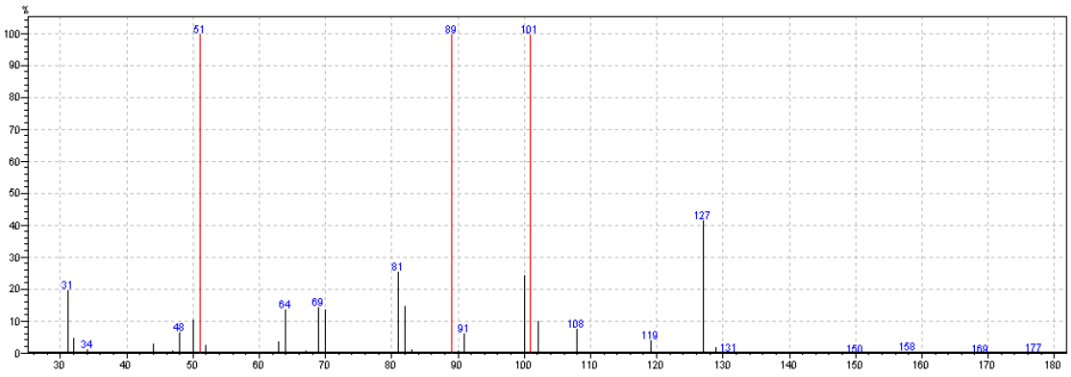

Figure A-21. *Mass spectrum of $SF_5CF_2CF_2H$.*

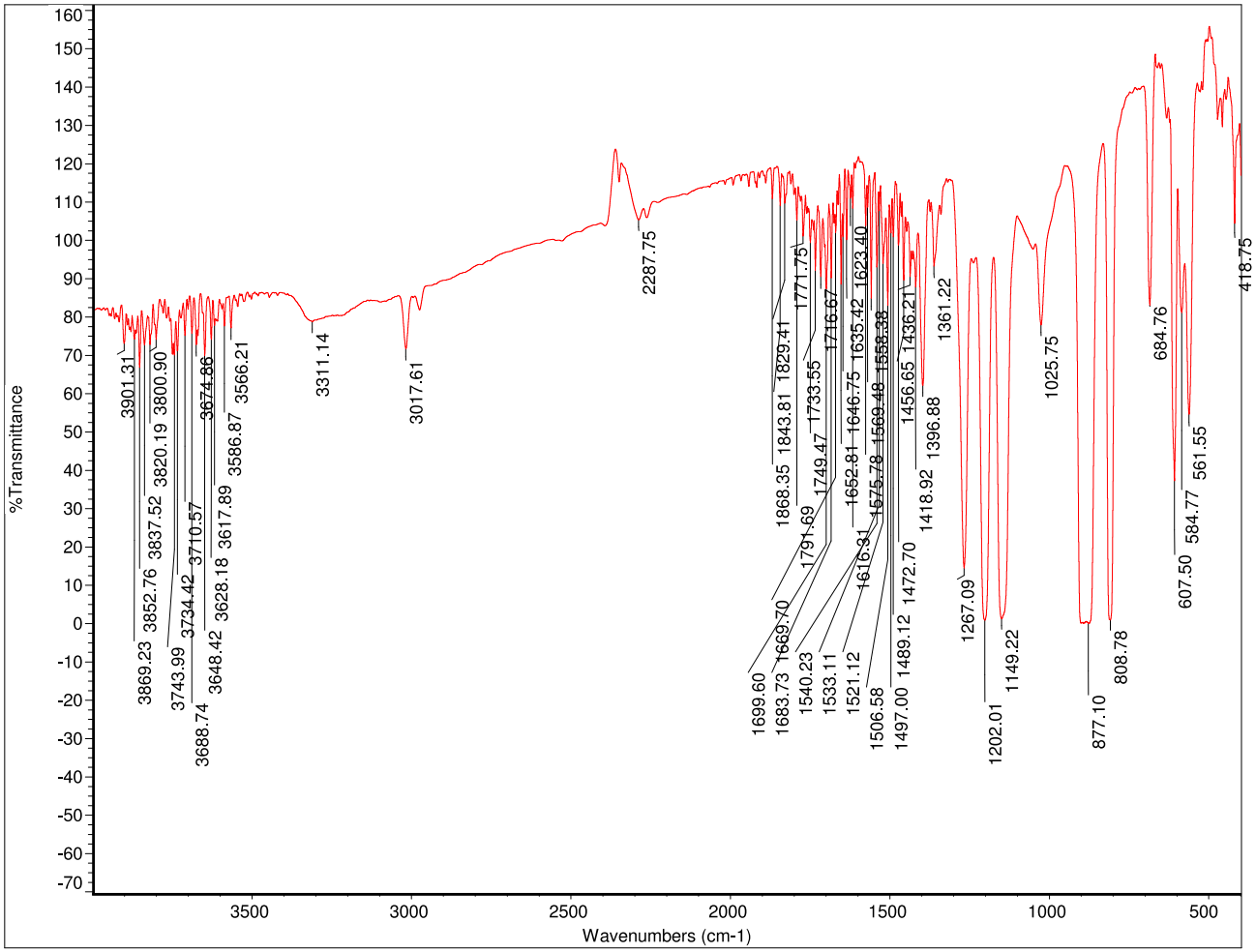

Figure A-22. *IR spectrum of the preparation of $SF_5CF_2CF_2H$.*

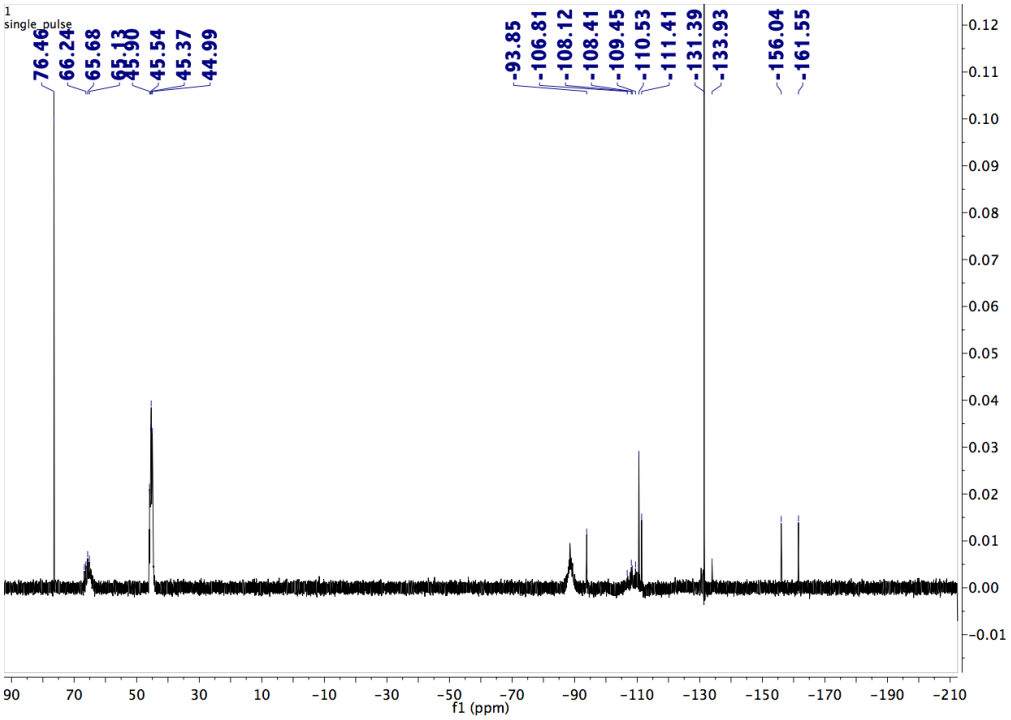

Figure A-23. *^{19}F NMR spectrum of the reaction mixture of $SF_5CF_2CF_2$-containing C_{60}/C_{70} prepared at 145 °C.*

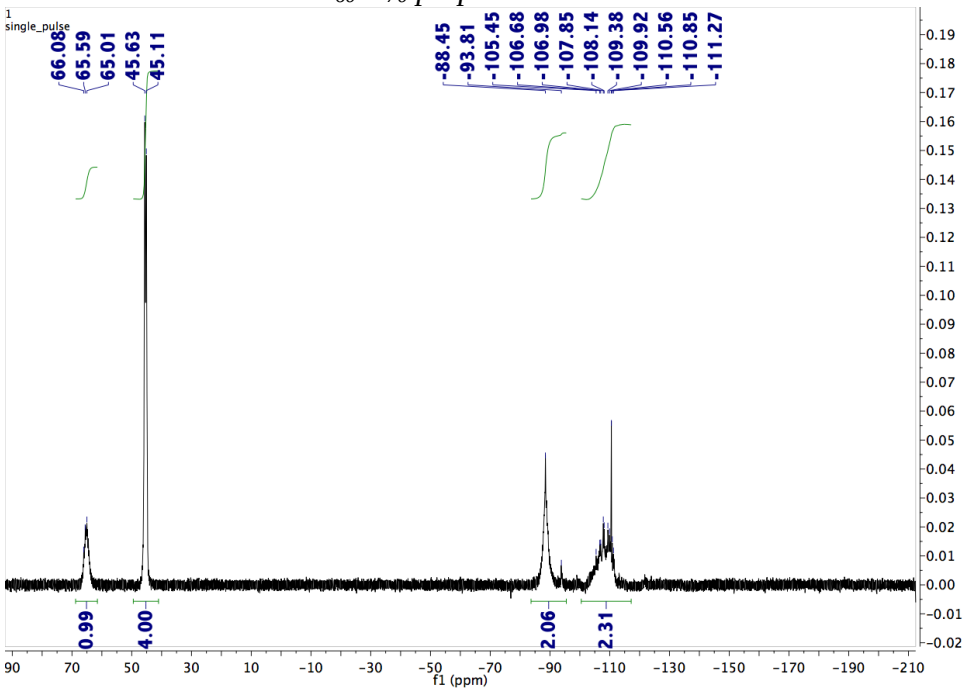

Figure A-24. *^{19}F NMR spectrum of the crude product of $SF_5CF_2CF_2$-containing C_{60}/C_{70} prepared at 145 °C.*

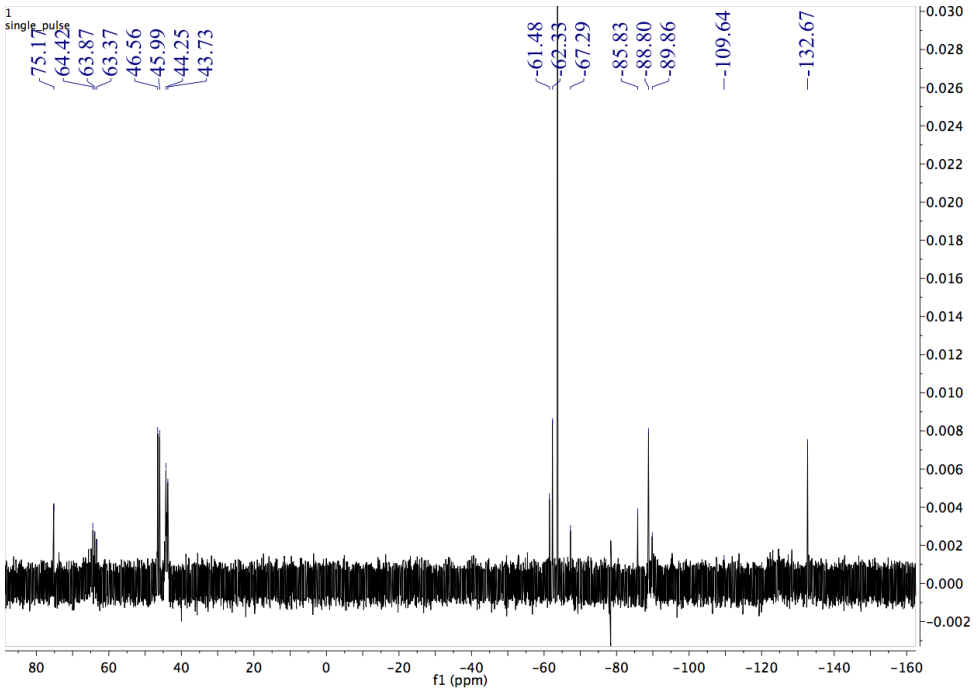

Figure A-25. *^{19}F NMR spectrum of the reaction mixture of $SF_5CF_2CF_2$-containing C_{60} prepared at 140 °C.*

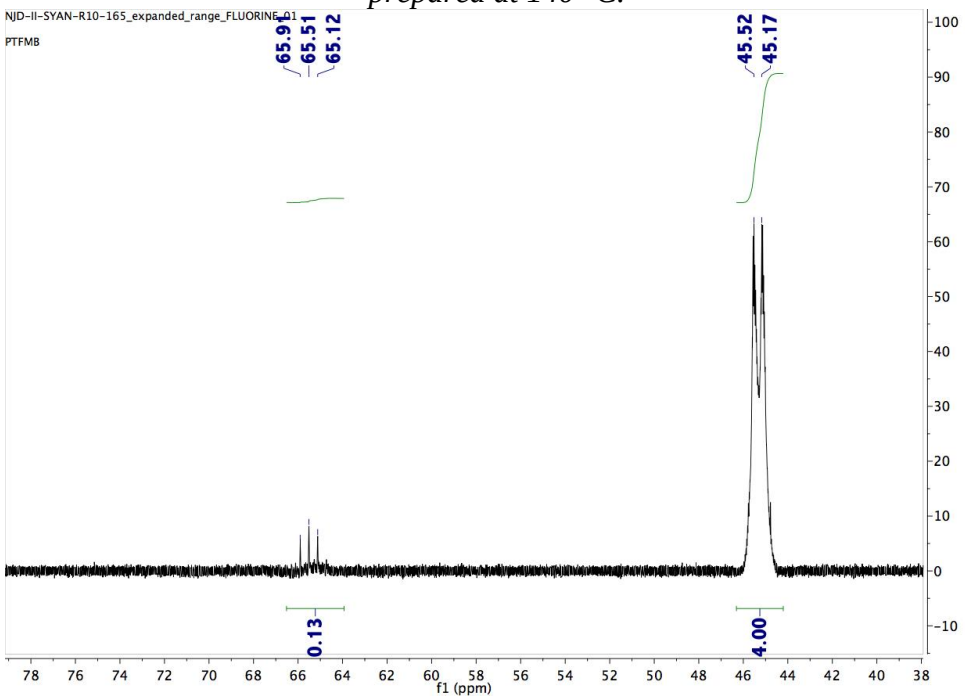

Figure A-26. *^{19}F NMR spectrum of the crude sample of $SF_5CF_2CF_2$-containing C_{60} prepared at 140 °C (SF_5 part).*

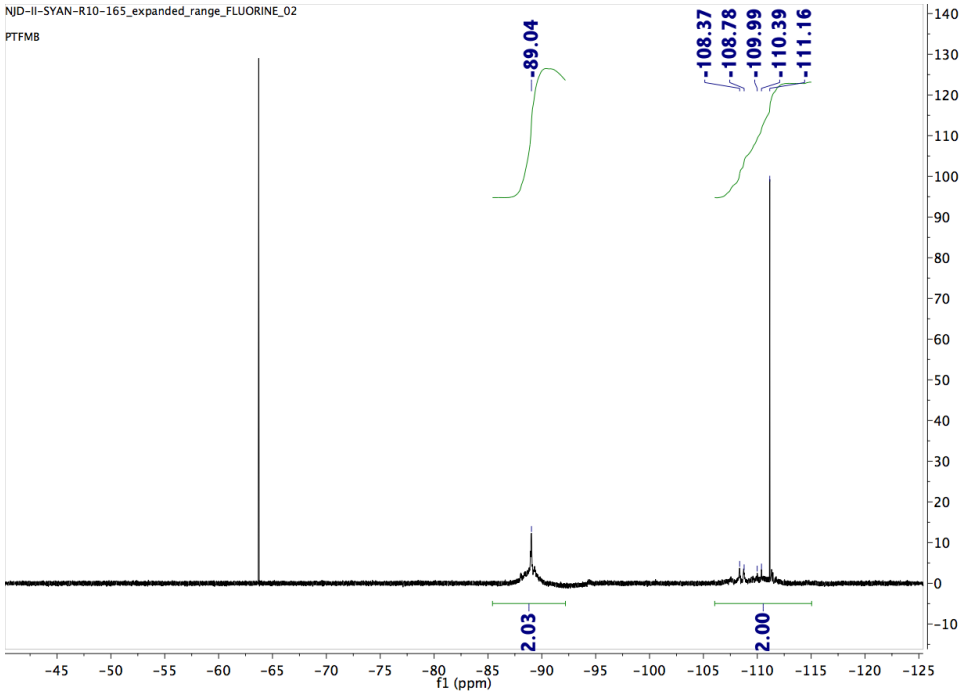

Figure A-27. *^{19}F NMR spectrum of the crude sample of $SF_5CF_2CF_2$-containing C_{60} prepared at 140 °C (CF_2CF_2 part).*

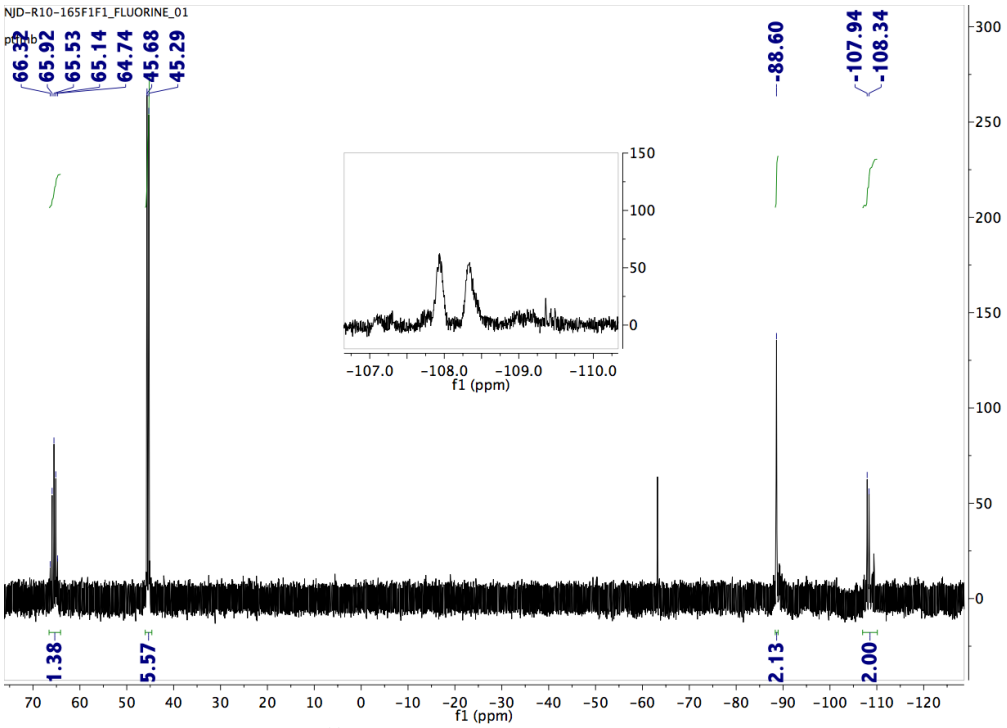

Figure A-28. *^{19}F NMR spectrum of bis-$(SF_5CF_2CF_2)_2$-C_{60}.*

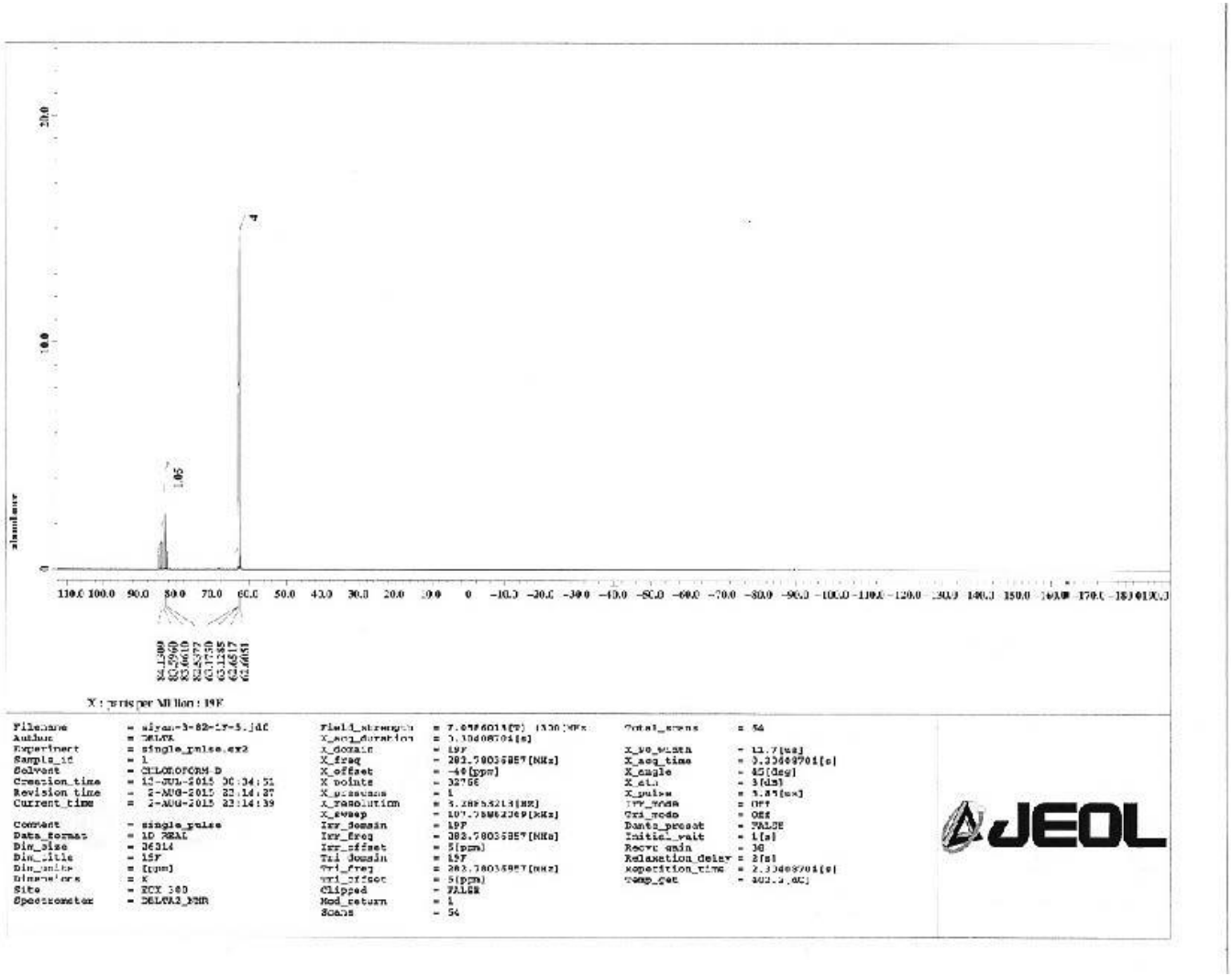

Figure A-29. *^{19}F NMR spectrum of 4-iodo(pentafluorosulfanyl)benzene.*

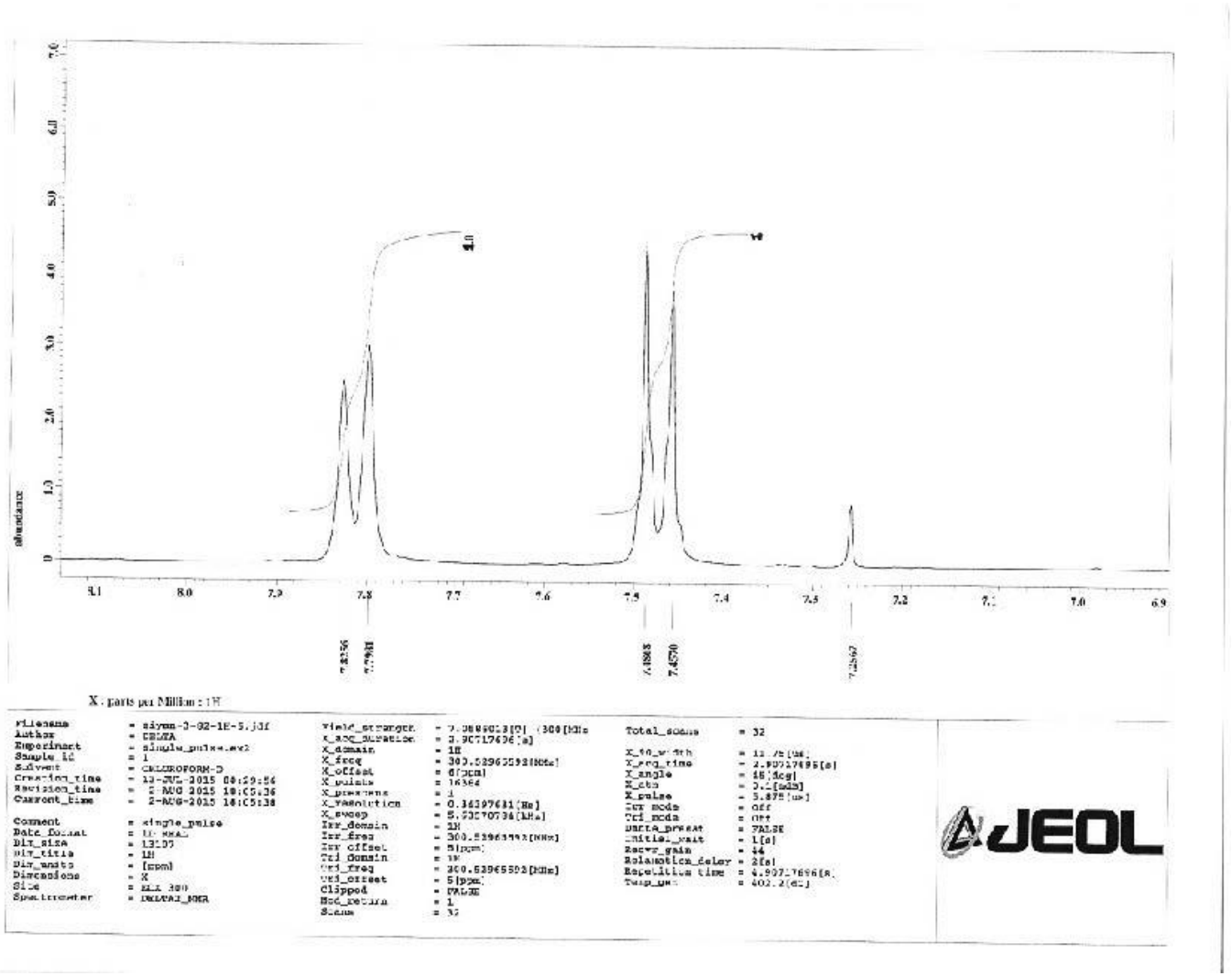

Figure A-30. *^{1}H NMR spectrum of 4-iodo(pentafluorosulfanyl)benzene.*

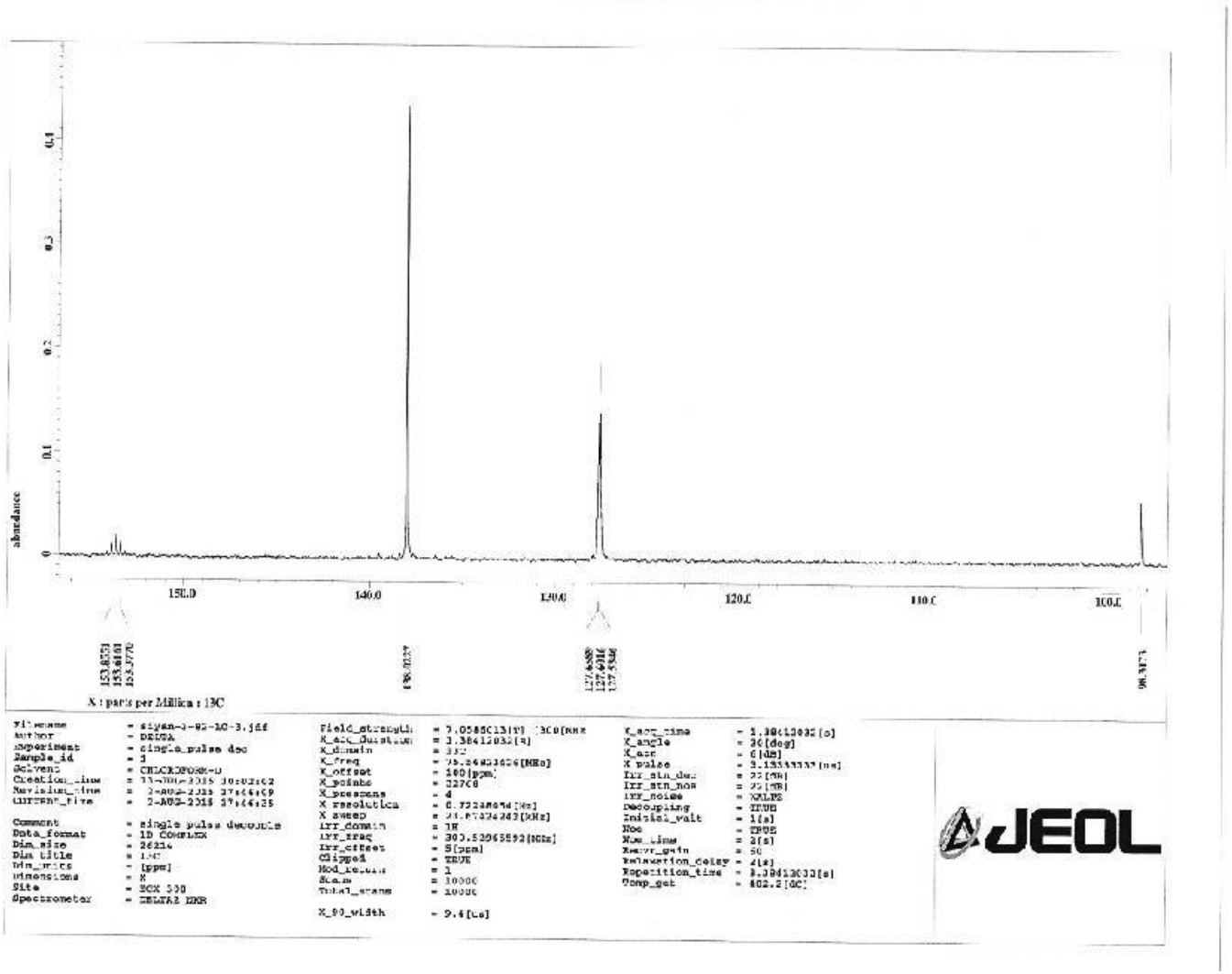

Figure A-31. *^{13}C NMR spectrum of 4-iodo(pentafluorosulfanyl)benzene.*